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Freise and Walenta³ in 1931 reported that the severing of the celiac plexus in young pigs produced a complex of symptoms which was characteristic of celiac disease.

Parsons⁴ in 1932 made the following statement: "Symptoms that are so severe and protracted as those occurring in well marked celiac disease should, if the disease be due to anatomic change, show very definite lesions."

A summary of the short abstract of the more important literature reveals that changes in almost every organ of the digestive tract and in the glands of internal secretion have been held responsible for celiac disease from time to time. If such changes were not found, primarily functional disorders were thought to be the causative factors.

CASE REPORTS

Three patients of whom a clinical diagnosis of celiac disease was made came under our observation. It does not fall within the scope of this communication to relate in detail the clinical findings and the differential diagnosis, therefore these findings are abstracted only briefly.

A postmortem examination was performed in each instance. Blocks were cut from the various organs fixed in 10 per cent formalin, and stained routinely with hematoxylin-eosin. Particular attention was paid to the thymus, suprarenals, thymus, liver, pancreas, and gastrointestinal tract. In addition to the hematoxylin-eosin preparations blocks of these organs were stained according to the van Gieson method for the presence of connective tissue. Silver stains were used (Foot's reticulum stain) to demonstrate reticulum fibers. Other sections were stained according to the Weir-Thomas method and examined for the presence of *Spirocheta pallida*. Frozen sections were cut and stained for fat with sudan III and sudan IV.

CASE 1—Onset and Course—The patient, a white female infant, aged nine months, weighed 7½ pounds at birth. There was a history of frequent bowel movements dating from shortly after birth. She was partially breast fed, with ample mental feedings of pasteurized milk until she was four and one half months old. At the time of weaning she was kept on cow's milk plus carbohydrates. She was first admitted to the hospital at five months of age, with a diagnosis of celiac disease. Up to this time there had been no serious illnesses other than intestinal disturbance as evidenced by frequent stools of large size, numbering from four to six daily. At five months she weighed 9 pounds 14 ounces. She was kept on a high protein diet and discharged after thirteen days in the hospital. She remained under observation for the following four months when, although on a high protein diet, she had several exacerbations of her intestinal trouble at which times she passed large, foul smelling stools averaging from four to six daily. She was again admitted to the hospital at nine months with a diagnosis of bronchopneumonia, at this time she weighed 12 pounds 4 ounces. The outstanding findings, other than the pneumonia, were emaciation and a markedly distended abdomen. She died twelve days after admission.

Autopsy Findings

Gross Changes—(Only the more important lesions will be described.) The body was that of a well developed but markedly undernourished white female infant about

ten months old. There was a bilateral bronchopneumonia with abscess formation. The liver was softer in consistency than normal and of about normal size. On section the architecture was slightly obscured, and the surface, grayish brown. Throughout the cut surface many minute, yellow, irregularly outlined dots were

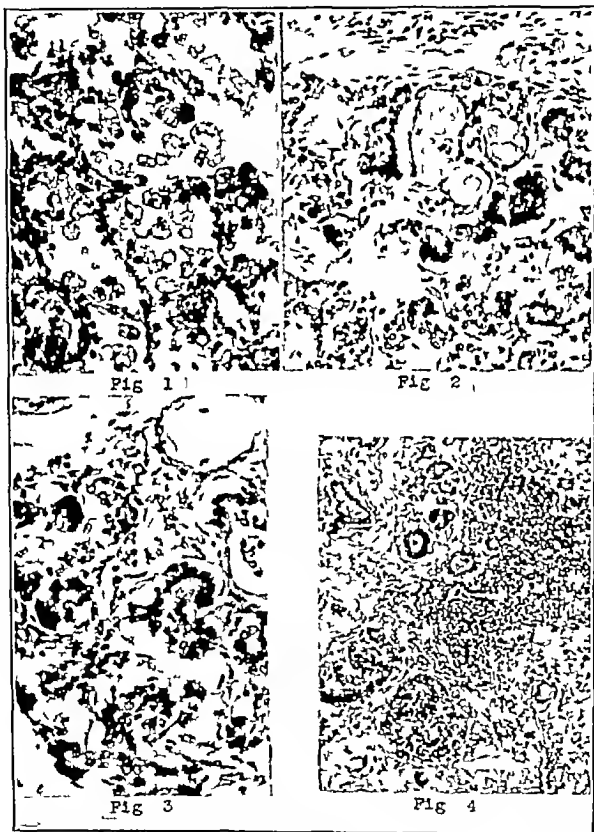


Fig 1—Case 1. Lung. Note the large fat-containing phagocytic cells within the alveoli. (Hematoxylin-eosin preparation, X250.)

Fig 2—Case 1. Pancreas. Fibrosis of the pancreas. Note the dilatation of the ducts, and the concretions. (Hematoxylin-eosin preparation, X300.)

Fig 3—Case 1. Pancreas. Note the apparently regenerated parenchymal cells. (Hematoxylin-eosin preparation, X250.)

Fig 4—Case 1. Pancreas. Lymphocytic infiltration and large islands of Langerhans. Note the early fibrosis of the islands. (Iron hematoxylin-eosin preparation, X120.)

seen, apparently situated in the central zones. The periportal spaces revealed no changes. The pancreas was hyperemic and slightly thicker than normal but otherwise presented no gross changes. The entire gastrointestinal tract was distended, the mucosa, thickened and finely granular in appearance. There was an excessive amount of a greenish mucus, which in some regions was firmly attached to the mucosa. There were no ulcers. The Peyer's patches and solitary follicles were swollen. The suprarenals were thin but otherwise appeared normal. Neither the thymus nor the thyroid revealed any gross changes.

Histologic Findings—Lungs. The alveoli contained a large number of polymorphonuclear leucocytes and also large monocyte cells revealing a clear or foamy cytoplasm and an eccentrically situated vesicular nucleus. The cytoplasm of these cells contained fat globules. Other alveoli contained red blood cells, a serum precipitate, and large clear cells similar to those just mentioned. A few fields revealed areas of necrosis with many clumps of bacteria. The bronchi were filled with polymorphonuclear leucocytes and desquamated lining cells.

Liver. Surrounding the central zones the liver cells contained many minute fat globules. These changes extended to about the midportion of the liver lobule. The periportal spaces were conspicuously free from fat.

Pancreas. The normal architecture of the pancreas was completely obscured. There was a marked new formation of connective tissue traversing the sections. The acini appeared very small, and in many instances groups of parenchymal cells were entirely separated from one another by newly formed connective tissue. The cytoplasm of the lining cells was often granular, and the outlines of the nuclei indistinct. Occasionally, mitotic figures were seen in these cells. The islands of Langerhans could easily be made out, many seemed enlarged. Very occasionally the newly formed connective tissue extended into the islands. The ducts in the sections were markedly dilated and many were filled with a granular material. In addition many ducts contained concentric pink stained bodies which could easily be interpreted as concretions. Warthin Starry stains failed to reveal spirochetes. Fat stains revealed a very small number of minute fat globules within the cells of the islands of Langerhans. The stroma revealed a slight infiltration of lymphocytes and a few polymorphonuclear leucocytes.

Small Intestines. Sections from the small intestines revealed the mucosa richly infiltrated with lymphocytes and a few polymorphonuclear leucocytes. A moderate new formation of connective tissue was seen in the submucosa, with a few endothelial cells, eosinophilic cells, and polymorphonuclear leucocytes.

The suprarenals, thymus, and thyroid revealed no histopathologic changes.

The main pathologic diagnosis was bronchopneumonia with abscess formation, chronic pancreatitis with much fibrosis, pancreatic lithiasis with dilatation of the ducts, chronic enteritis, and fat infiltration of the liver (centrally located).

CASE 2—Onset and Course—The infant, a white male, aged eighteen months, had frequent bowel movements from birth until six months of age, often averaging twelve or more per day, and composed largely of mucus and curds. After six months the stools were more normal in color but large in amount, at times fairly well formed, and always with a bad odor. Vomiting was also frequent up to the third month.

Feeding History—Until two months of age the infant was on breast milk, complemented by cow's milk and dextrinmaltose. During the third month he had supplementary feedings of protein milk, and from the third to the sixth month, protein milk alone. At this time he was placed on goat's milk for one month, then on

Carnation milk until he was nine months old when he weighed 16 pounds 10 ounces. At nine months he developed tonsillitis and lost 1 pound 7 ounces in weight.

He was first admitted to the hospital at ten and one-half months. He was a small but fairly well nourished infant. Further positive physical findings were flaring of the lower ribs with moderate beading. The abdomen was large and tense. There was moderate epiphyseal enlargement.

Clinical diagnosis was rickets and chronic intestinal indigestion. The possibility of a food allergy was given serious consideration.

The child was discharged after ten days in the hospital and was readmitted at eighteen months. During the interval the child had been on a high protein diet consisting of protein milk, eggs, cottage cheese, orange juice, bananas, and more recently, small amounts of vegetables, together with cod liver oil and viosterol. He was readmitted with a diagnosis of influenza pneumonia and died on the third day after admission.

Autopsy Findings

Gross Changes.—The patient was a well developed, markedly undernourished white male infant about eighteen months old. There was a bilateral bronchopneumonia.



Fig. 5.—Case . . . Pancreas marked fibrosis. (Hematoxylin-eosin preparation $\times 60$)

The liver was slightly enlarged. On section the surfaces were brownish gray. Throughout the surfaces were seen minute yellow dots which were confined to the central zones. The periportal spaces showed no gross changes. The pancreas presented no gross abnormalities. The mucosa of the stomach was pale and the rugae flattened. The mucosa of the duodenum and upper jejunum was hyperemic. The Peyer's patches and solitary follicles were swollen and slightly granular. The mucosa of the distal ileum was thrown into folds and covered with an excessive amount of mucus. The jejunum measured 300 cm. in length, the ileum, 50 cm., while the entire intestinal tract measured 457 cm. The mesenteric nodes were enlarged and soft, presenting pink surfaces. The suprarenals, thymus, and thyroid showed no gross changes.

Histologic Findings.—Lungs. Sections revealed many of the alveoli containing polymorphonuclear leucocytes in addition to large macrocytic cells showing a foamy cytoplasm and a slightly eccentrically situated nucleus. These cells were filled with fat, as could be demonstrated by special stains.

Liver. Surrounding the central veins the liver cells appeared foamy and many of them contained minute fat globules.

Pancreas The normal architecture of the pancreas was completely destroyed. Pancreatic parenchyma could be recognized in only a few fields in each section. There was a marked new formation of connective tissue separating small tubuli from one another. Many of the cells lining the acini showed indistinctly stained nuclei and a granular cytoplasm. There were, however, cells present which showed hyperchromatic nuclei, and occasionally mitotic figures were recognized in these cells. The islands of Langerhans seemed larger than normal and showed many hyperchromatic nuclei. Occasionally, a moderate amount of connective tissue was also seen within the islets. Small fat granules could be seen in some of the islet cells. The ducts in the sections were markedly distended and many contained a reddish granular debris. Here and there were seen a varying number of pink stained concentric bodies, which gave the impression of concretions. Other ducts contained desquamated lining cells. The stroma consisted of connective tissue fibers, some of which seemed hyalinized. Only a few fibroblasts were seen. Here and there, a slight infiltration of lymphocytes and very few polymorphonuclear leucocytes could be made out. Spirochetes could not be demonstrated.

Small Intestines Sections of the small intestines revealed a moderate infiltration of lymphocytes, endothelial cells, and a few polymorphonuclear leucocytes. There was a marked new formation of connective tissue in the submucosa. The lymph follicles, particularly in the region of the jejunum, were hyperplastic, their centers revealing much karyorrhexis and karyolysis.

Suprarenals, Thyroid and Thymus No histopathologic changes were noted.

The main pathologic diagnosis was bronchopneumonia, recent, chronic pancreatitis with much fibrosis, pancreatic lithiasis, dilatation of the pancreatic ducts, chronic enteritis, abnormal length of the jejunum, and fat infiltration of the liver (centrally located).

CASE 3—The patient, a white female child, aged three years, was admitted to the hospital for the first time at seven months.*

Onset and Course—She was breast fed for two weeks, following which she was given a cow's milk formula for two months, and during the following six weeks was placed on various other formulas, because of unsatisfactory gain in weight. At four months she developed her first attack of diarrhea, which continued for one month. Following this, her progress was fair for three weeks, when she again developed diarrhea.

She was admitted to the hospital for the second time when she was three years old. Between her fifth month and third year her progress had been slow, and she had recurrent attacks of intestinal indigestion and diarrhea. She had pneumonia at one and one half years and measles at two and one half years. Her history was otherwise negative except for the gastrointestinal disturbances.

The admission diagnosis on the day before her death was anhydremic intoxication, celiac disease, and athrepsia.

Autopsy Findings

Gross Changes—The body was that of a well developed but markedly undernourished white female appearing to be two years old. The lungs revealed bilateral bronchopneumonia. The architecture of the liver was indistinct, and no details as to central zones or periportal spaces could be made out. The surfaces were yellowish. The pancreas showed no gross changes. A few diverticula were present in the stomach. The ileum showed enlarged follicles and Peyer's patches, which were granular and distinctly raised. The mucosa was slightly thicker than normal.

*We are indebted to Dr. I. A. Abt for the use of the clinical record.

and was covered with an excessive amount of mucus. The mesenteric nodes were enlarged, soft, revealing pink surfaces. The left kidney showed an irregular golden brown rather soft stone measuring 5 mm. in diameter. No gross changes were found in the suprarenals, thyroid and thymus.

Histologic Findings—Lungs. Sections revealed many of the alveoli filled with large mononuclear cells showing a clear cytoplasm which contained large fat globules. Many of the alveoli were completely filled with these phagocytic cells. Other alveoli contained polymorphonuclear leucocytes.

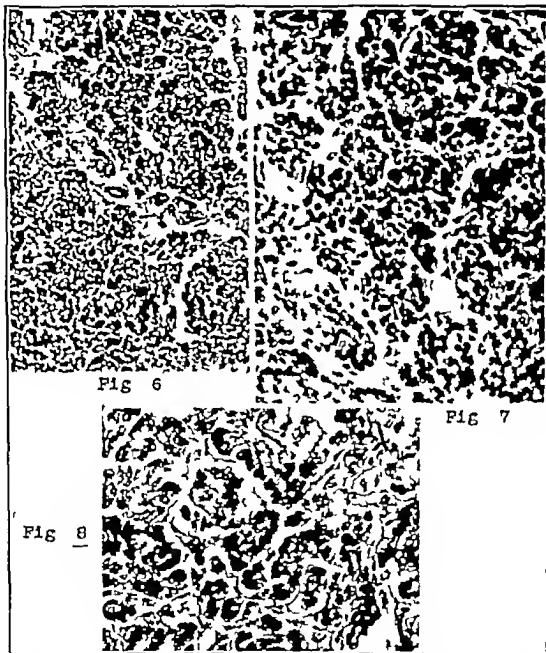


Fig 6—Case 3. Pancreas. Note the increase in connective tissue. (Van Gieson preparation, $\times 80$)

Fig 7—Case 2. Pancreas. Note the large cellular masses without the formation of regular acini. (Iron hematoxylin-eosin preparation $\times 250$)

Fig 8—Case 3. Pancreas. Note the dense reticulum fibers. (Reticulum stain, $\times 300$)

Liver. The cytoplasm of the parenchymal cells throughout the liver showed many large fat globules and also many minute fatty droplets. The changes seemed more pronounced in the region of the central zones but were present throughout.

Pancreas. Hematoxylin-eosin stains revealed a distinct new formation of connective tissue throughout the pancreas which, however, was far less pronounced than in Cases 1 and 2. The lobules were clearly recognizable in many fields and

only in some sections were the acini traversed by connective tissue. The pancreatic cells throughout appeared smaller than normal but revealed very prominent nuclei. The cytoplasm in many fields was indistinct, and the differentiation between individual cells was difficult. In several instances, masses of nuclei of pancreatic parenchyma appeared as a syncytium. The lumina of the tubuli in many fields were indistinct. The islands of Langerhans were clearly recognizable. They seemed larger than normal but showed no changes. The ducts throughout the sections were surrounded by newly formed connective tissue, which occasionally revealed a moderate number of lymphocytes and very few polymorphonuclear leucocytes. Some of the ducts were dilated and contained desquamated cells, but no concretions were noticeable. The van Gieson stain revealed a new formation of connective tissue, in many fields separating the tubuli from one another. The changes were much more severe than could have been judged from the hematoxylin-eosin stain. A large amount of reticulum fibers could be demonstrated by the silver stain. These fibers often completely encircled the individual parenchymal cells. No spirochetes were found.

Small Intestines. Sections taken from the small intestines revealed many lymphocytes and plasma cells, and occasional polymorphonuclear leucocytes in infiltrating the mucosa and submucosa. There was a slight new formation of connective tissue in the submucosa, particularly pronounced in the ileum.

Suprarenals, Thymus, and Thyroid. Sections of these organs revealed no histopathologic changes.

The main pathologic diagnosis was bronchopneumonia, fibrosis of the pancreas, nephrolithiasis, multiple diverticula of the stomach, chronic gastroenteritis, and fat infiltration of the liver (diffuse).

DISCUSSION

The postmortem findings in these three instances were strikingly similar. The autopsies revealed bronchopneumonia of recent development, chronic enteritis, and severe changes in the pancreas in every instance. The cause of death was the bronchopneumonia. In view of the general malnutrition it is easily understood why the infants died of the bronchopneumonia, even though it was not very extensive in one instance.

Unusual histologic findings in the alveoli of the lungs in these cases were the large monocyte cells which were filled with fat. It is possible that the presence of the large phagocytes filled with fat signifies metabolic changes affecting particularly the fat metabolism.

The thymus, thyroid, and suprarenals showed no gross or histologic changes in any of the cases. Schick and Wagner,¹⁸ who found marked atrophy of the thymus, suprarenals, and pancreas, believed that in instances of celiac disease it was an "anatomically proved fact that glands of internal secretion which are in close relationship to digestion are primarily atrophic." They coined the term "atrophia pluriglandularis digestiva." Their findings, however, could not be confirmed by Fanconi,²⁸ Bloch,²⁹ and others. We also could find no evidence of atrophy of the thymus, thyroid, and suprarenals.

Chronic lesions were found in the intestinal tract, principally affecting the small intestines. In none of our cases, however, were the changes very severe or apparently of long duration. It is, therefore, doubtful that these lesions, though present in every instance, were the cause of celiac disease. It seems more likely that they were the result of changed intestinal contents and secondary infection. There were no ulcers, no scars, but a chronic catarrhal inflammation, which in some instances could not have been diagnosed without a histologic examination. It would be difficult to understand why such lesions should lead to the significant wastage of fat.

The seemingly enlarged jejunum which was encountered in the second case may be explained on the basis of the nutritional disturbance of long duration (Mantner and Lelendorf²).

Grossly the pancreas showed no noteworthy changes in any of the cases. It was slightly firmer than normal in one instance, but not sufficiently to attract special attention to it. The pancreatic ducts were not dissected grossly. Histologically, the changes in the pancreas were marked. A severe fibrosis was encountered in two instances, with dilated ducts and seemingly large islands of Langerhans, some of which also revealed an increase of connective tissue. Scattered throughout was a slight lymphocytic infiltration. In Case 3 the changes as encountered in the hematoxylin-eosin preparations were much less severe, and only by the use of special staining methods, a distinct new formation of connective tissue and reticulum often encircling parenchymal cells was encountered. Inflammatory cells were not numerous. This may indicate that the inflammation—provided that the fibrosis was the result of a primary inflammation—had subsided. It is likewise possible that the fibrosis was not the result of a primary acute inflammation but followed a primarily chronic irritation such as the closure of the duct. In addition to the marked fibrosis, the pancreas revealed a dilatation of the ducts in every instance, with periductile fibrosis and relatively large islands of Langerhans. In the first two instances, concretions were also demonstrable within the ducts.

Syphilis as the cause of pancreatic changes could be ruled out. Neither were the histologic changes suggestive of syphilis nor were spirochetes demonstrable. While it may be possible that primary concretions in the ducts which were found in the first two instances could explain the changes in the pancreas, we have no proof that the concretions were primarily present. It is likewise possible, however, that because of primary inflammatory changes of the smaller ducts, with closure of some and dilatation of others, concretions were formed secondarily.

In all three instances, evidence of regeneration of the pancreas was demonstrated by the presence of mitotic figures and by the appearance of syncytial cell masses in the pancreas in the third case, which showed the least change. It seems likely that in this case the pancreatic

parenchyma regenerated but the fibrosis still persisted. The first two infants died before the regeneration had taken place, but it is likewise possible that the changes in these instances were so severe that complete regeneration could not have occurred. It may be mentioned in this connection that Giubet,³³ summarizing the evidence for regeneration of the pancreas, stated recently that regeneration of the pancreas is a proved fact.

Parsons² stated that "in two or three cases some excess in fibrous tissue or small cell infiltration around the ducts of the pancreas" was found in instances of celiac disease. On the other hand, he stated that "the finding after much scratching about of some small grains of reward in the shape of an alteration in a few cells does not seem sufficient to justify an exalting cackle." From the point of view of the morphologist, however, it must be stated that excess in fibrous tissue and small cell infiltration are important. While these changes may seem insignificant at the time of examination, they constitute a document of a past insult and indicate that more severe lesions which have subsided were present some time ago. It is conceivable that the initial lesions subsided and only scars remained here and there, while other portions of the pancreas regenerated. It must be conceded that other cases of celiac disease, showing what was interpreted as slight changes by the use of the hematoxylin eosin stain, also fall into this group.

Even if the pancreatic changes were the prime factor in the production of the clinical symptoms, recovery is explainable on the basis of the ability of the pancreas to regenerate acini and islets.

It is extremely difficult to decide whether a difference exists between primary pancreatic disease in infancy and the clinical picture of celiac disease or whether both are identical. Burghard's,³⁴ Gross's,²⁷ and Passini's¹⁰ cases which revealed severe changes in the pancreas are regarded as examples of celiac disease. The changes in the pancreas in Gross's case were almost identical with those seen in our first two cases. In our opinion the most outstanding clinical symptoms of celiac disease, namely, the wastage of fat, can be explained on a primary pancreatic disorder. Because of the changes of the pancreas, we believe that it is also possible to correlate the changes in the carbohydrate metabolism in these cases on the basis of a pathologic pancreas. The hypophysis, unfortunately, could not be examined.

It may be mentioned in this connection that Gross²⁸ and, also, Nakamura³⁵ stated that systematic examination of the pancreas in children revealed that atrophy of the pancreas may occur in instances of diseases of the gastrointestinal tract and in acute and chronic toxic conditions. Also, Parsons² remarked that the changes in the pancreas "are either due to secondary infection or are the result of malnutrition." On the other hand, however, Gross,²⁷ and likewise Nakamura³⁵ stressed

that a primary disease of the pancreas may lead to severe malnutrition of the patient. Gross's²⁵ case and our three cases, we believe, belong to this latter group.

We are well aware of the fact that instances of celiac disease are described in the literature, which reveal chronic diseases of the gastrointestinal tract but no changes in the pancreas. If, by the use of special staining methods, it is not possible to demonstrate fibrosis in the pancreas, then it must be conceded that the symptom-complex of celiac disease has not one definite pathologic entity. Our series comprising only three instances, is too small to permit generalization. Because of our findings we must insist, however, that in every instance of celiac disease the pancreas should be studied with the before mentioned special methods before pronouncing it normal.

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ATHLETIC PERFORMANCE AS A FUNCTION OF GROWTH SPEED IN SPRINTING

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AMONG the many problems of physiology basic to clinical medicine to which investigators in recent years have devoted so much attention, those of metabolism and growth have come to occupy an increasingly important place in the interest of pediatricians. The various aspects of growth in particular have been extensively studied and in many instances found to be susceptible of orderly analysis and even reduction to mathematical formulas. This is true of both the static and of the dynamic aspects of growth of size of the body and its parts and of its faculties or functions. Of the latter, speed in sprinting is an important representative and forms the subject of the present report.

In sprinting the tempo is important because physiologically the "quickest way to reach the winning post is to take at the outset that speed which will just produce exhaustion at the goal and keep that speed throughout the course. The penalty for raising the speed at any part would be a degree of untimely exhaustion far outweighing the benefit gained" (Kennelly¹). The distance divided by the time may therefore be regarded as the individual's optimum speed for the particular event. It follows that for other distances that individual's optimum may be better. Furthermore, if we pick out the fastest speed recorded in any competitive event (namely, 9.906 meters per second in the 130-yard record made in 1911), we obtain a value which is better, because it is a human rather than an individual optimum. In its turn even this value is less than the maximum speed so far recorded for a running man at any moment, namely 10.48 meters per second, between 45 and 50 yards, as measured with electric coils along the course. (Hill and his pupils, 1927²)

Observations—The runners were boys from the ages of nine years to twenty years and six months at the Tamalpais School in San Rafael, Calif. The track was of firm grass, on a slight slope, such that the running time for a number of boys was the same as on a cinder track, in fact the fastest performer did slightly less well than on cinders. The starting signal was "get ready," then a gun. The observations were made by F. J. D., whose experience in varsity athletics and as a coach extends over many years. Ages were recorded to the nearest

From Stanford University School of Medicine, aided by the Rockefeller Fluid Research Fund.

month (e.g., a boy of 9 years $4\frac{3}{4}$ months was recorded as 9 years 5 months), and the ages were tabulated in groups of six months, beginning with 9 years to 9 years 6 months, midpoint at 9.25 years. Times were taken in seconds and fifths (e.g., 9 and $\frac{1}{5}$ meant 9 and $\frac{1}{5}$ but less than 10 seconds), these observations were converted into decimals (e.g., 9.8 seconds), and grouped in class-intervals of 0.4 second, beginning with the class 9.6 and less than 10.0, midpoint at 9.8 seconds. The averages and other reduced statistics on the 992 observations are listed in Table I.

Spot Chart of Observations—The raw data and also the averages for age are plotted in the diagram—age along the horizontal axis, time on the right vertical scale, and on the left vertical is speed in meters per second. The solid dots emphasize the notable variation in performance among boys within any six months-age-group. The circles represent the averages for the age groups, and from now on we shall deal mainly with the averages. The next step is to smooth them, and this has been done by a line through the field of plotted points, hence for any given boy we may find his age on the baseline and read up to the curve and then sideways to find the average, or so-called "normal," running time on the right vertical scale or speed on the left.

The crossed averages, which stray so markedly from the stream, are explicable as follows. The high value at 20.25 years represents two boys who were exceptional, not ordinary performers. The three values below the right end of the curve, namely for 19.75, 19.25, and 18.75 years, reflect the noteworthy tendency of some boys in the last year or two of school to act bored with tests and let down in effort—the same phenomenon is found in other tests. After these four crossed circles are omitted there remain nineteen means covering 966 observations for further analysis.

Theory for the Curve—In order to graduate the observations for practical use, a trend line was sketched freehand. It took the form of an elongated "S." Now growth phenomena, too many to review here (though traceable through the references at the end of this paper), have been thought to fit either a logistic or a Gompertz curve, either of which has the convenience of a small number of constants. Formulas with various assumptions for the constants were tested (on Wilson's² grid paper for the logistic, on Curtis's⁴ grid for the Gompertz), until an equation was found which nearly coincided with the tentative free hand curve and was then substituted in the graph. This preferred law was the so-called autocatalytic, or speaking more generally and without conjecture as to chemical kinetics, the logistic. Indeed it is presented mainly as a neat and useful interpolation formula. Its limitations have been acutely analyzed by Wilson and Puffer 1933,⁵ by Kavanagh and Richards 1934.⁶

TABLE I
100 YARD DASH—STATISTICS ON 992 OBSERVATIONS

AGE		NUMBER OF OBSERVATIONS	TIME SECONDS PER 100 YD (91.44 M.)					SPEED IN METERS PER SECOND
CLASS LIMITS	MIDPOINT		f	MEAN	PROBABLE ERROR OF MEAN	STANDARD DEVATION	COEFFICIENT OF VARIATION	
YEARS AND TENTHS	YEARS	(3)	SEC (4)	SEC (5)	SEC (6)	% (7)	M / SEC (8)	
90 - 95	9.25	6	16.9	0.22	0.81	4.8	5.40	
95 - 100	9.75	8	15.9	0.23	0.96	6.0	5.74	
100 - 105	10.25	10	16.7	0.29	1.35	8.1	5.48	
105 - 110	10.75	28	15.9	0.14	1.10	6.9	5.77	
110 - 115	11.25	29	16.4	0.17	1.35	8.2	5.57	
115 - 120	11.75	46	15.5	0.12	1.22	7.9	5.90	
120 - 125	12.25	40	15.3	0.11	1.00	6.5	5.97	
125 - 130	12.75	53	15.1	0.13	1.39	9.2	6.06	
130 - 135	13.25	54	15.0	0.12	1.30	8.9	6.22	
135 - 140	13.75	66	14.3	0.13	1.52	10.6	6.37	
140 - 145	14.25	87	13.9	0.09	1.29	9.2	6.57	
145 - 150	14.75	71	13.5	0.13	1.58	11.6	6.76	
150 - 155	15.25	98	13.3	0.09	1.34	10.0	6.85	
155 - 160	15.75	84	12.8	0.09	1.25	9.7	7.14	
160 - 165	16.25	85	12.8	0.10	1.37	10.7	7.15	
165 - 170	16.75	67	12.4	0.10	1.24	10.0	7.39	
170 - 175	17.25	65	12.0	0.08	1.01	8.4	7.64	
175 - 180	17.75	44	12.3	0.11	1.09	8.9	7.44	
180 - 185	18.25	25	11.9	0.12	0.88	7.4	7.66	
185 - 190	18.75	16	12.4	0.17	1.00	8.0	7.37	
190 - 195	19.25	6	12.1	0.21	0.78	6.4	7.56	
195 - 200	19.75	2	12.5				7.32	
200 - 20.5	20.25	2	10.6				8.63	

For visual comparison with other material following the logistic law, it is convenient to follow Yule's⁷ scale and proportions for the universal logistic, with *age* on the baseline calibrated in tau units. Greek letter τ , multiples of the standard interval measuring, to the left or right (minus or plus) from the age of inflection and on the vertical scale *speed* expressed first in meters per second and then converted into percentage of an assumed maximum speed at completed growth.

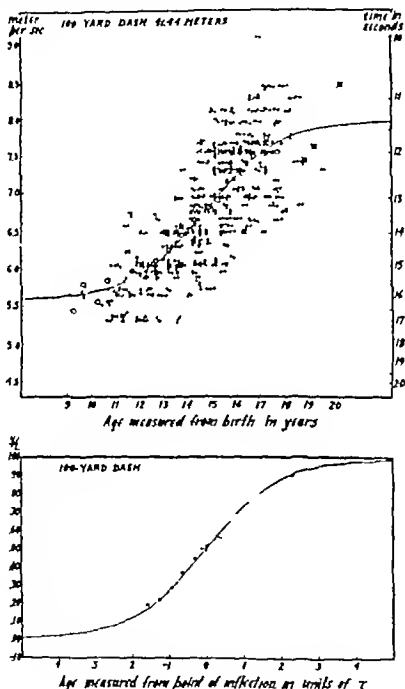


FIG 1

For the present material this upper asymptote is the maximum expected for the average performance of a group of boys not the maximum approached by the group's fastest individual. When observations have been obtained on such an individual runner, say from the age of nine to the age of twenty his growth in speed will follow a different curve, and if that curve be a logistic it will certainly approach a higher maximum than that of the present group curve. Numerically that in

TABLE I
100 YARD DASH—STATISTICS ON 902 OBSERVATIONS

AGE		NUMBER OF OBSERVATIONS	TIME SECONDS PER 100 YD (91.44 M.)					SPEED IN METERS PER SECOND
CLASS LIMITS	MIDPOINT		f	MEAN	PROBABLE ERROR OF MEAN	STANDARD DEVIATION	COEFFICIENT OF VARIATION	
YEARS AND TENTHS	YEARS	(1)	(4)	(5)	(6)	(7)	M / SEC (8)	
90 - 95	9.25	6	16.9	0.22	0.81	4.8	5.40	
95 - 100	9.75	8	15.9	0.23	0.96	6.0	5.74	
100 - 105	10.25	10	16.7	0.29	1.35	8.1	5.48	
105 - 110	10.75	28	15.9	0.14	1.10	6.9	5.77	
110 - 115	11.25	29	16.4	0.17	1.35	8.2	5.57	
115 - 120	11.75	46	15.5	0.12	1.22	7.9	5.90	
120 - 125	12.25	40	15.3	0.11	1.00	6.5	5.97	
125 - 130	12.75	53	15.1	0.13	1.39	9.2	6.06	
130 - 135	13.25	54	15.0	0.12	1.30	8.9	6.22	
135 - 140	13.75	66	14.3	0.13	1.52	10.6	6.37	
140 - 145	14.25	87	13.9	0.09	1.29	9.2	6.57	
145 - 150	14.75	71	13.5	0.13	1.58	11.6	6.76	
150 - 155	15.25	98	13.3	0.09	1.34	10.0	6.85	
155 - 160	15.75	84	12.8	0.09	1.25	9.7	7.14	
160 - 165	16.25	85	12.8	0.10	1.37	10.7	7.15	
165 - 170	16.75	67	12.4	0.10	1.24	10.0	7.39	
170 - 175	17.25	65	12.0	0.08	1.01	8.4	7.64	
175 - 180	17.75	44	12.3	0.11	1.09	8.9	7.44	
180 - 185	18.25	25	11.9	0.12	0.88	7.4	7.66	
185 - 190	18.75	16	12.4	0.17	1.00	8.0	7.37	
190 - 195	19.25	6	12.1	0.21	0.78	6.4	7.56	
195 - 200	19.75	2	12.5				7.32	
200 - 205	20.25	2	10.6				8.63	

Agreement of Observation With Theory—The deviations of the observed means from the corresponding values on the curve of theory have been computed $\gamma_o - \gamma_t = \Delta$, and these deltas treated in four ways which have been used by one or another of the investigators of the logistic. The results are satisfactorily small

$$\begin{aligned} \text{Root mean square-deviation} &= \sqrt{\frac{\sum (\Delta^2)}{19}} = 0.093 \text{ m./sec.} \\ \text{Weighted root mean square-deviation} &= \sqrt{\frac{\sum (f \Delta^2)}{906}} = 0.080 \text{ m./sec.} \\ \text{Percentage-deviation of observation from theory} &= \frac{\sum \left(\frac{100 \Delta}{\gamma_t} \right)}{19} = 1.22 \text{ per cent} \\ \text{Weighted percentage-deviation of observation from theory} &= \frac{\sum \left(\frac{f 100 \Delta}{\gamma_t} \right)}{900} = 0.57 \text{ per cent} \end{aligned}$$

Standards for Practical Use—Athletic performance standards are commonly stated with regard to school grades. Now a given grade in

TABLE II
100 YARD DASH PREDICTED STANDARD FOR PRACTICAL USE

AGE IN YEARS AND TENTHS	EXPECTED TIME IN SECONDS AND TENTHS (LONGEST TIME FOR GROUP INDICATED)				
	FASTEST 2% OF BOYS	FASTEST 16% OF BOYS	FASTEST 50% OF BOYS (AVERAGE OF ALL)	FASTEST 84% OF BOYS	FASTEST 98% OF BOYS
(1)	(2)	(3)	(4)	(5)	(6)
9.0	16.0	16.8	16.6	17.4	18.2
9.5	14.8	15.0	16.5	17.4	18.2
10.0	14.5	16.4	16.4	17.4	18.3
10.5	14.1	16.2	16.2	17.3	18.3
11.0	13.7	14.9	16.0	17.1	18.3
11.5	13.4	14.0	15.8	17.0	18.2
12.0	13.0	14.3	15.0	16.9	18.2
12.5	12.5	13.9	15.2	16.6	17.9
13.0	12.1	13.5	14.9	16.3	17.7
13.5	11.6	13.0	14.5	16.0	17.4
14.0	11.1	12.6	14.1	15.6	17.1
14.5	10.7	12.2	13.8	15.4	16.9
15.0	10.4	11.9	13.4	14.9	16.4
15.5	10.2	11.6	13.0	14.4	15.8
16.0	10.1	11.4	12.7	14.0	15.3
16.5	10.1	11.3	12.5	13.7	14.9
17.0	10.0	11.1	12.2	13.3	14.4
17.5	10.0	11.1	12.1	13.2	14.2
18.0	9.9	10.9	11.9	12.9	13.9
18.5	9.9	10.9	11.8	12.7	13.7
19.0	9.9	10.8	11.7	12.6	13.5
19.5			11.6		
20.0			11.6		
20.5			11.5		

The standard deviations used to determine percentiles in this table were read from a smooth curve drawn on a plot (not reproduced) of the computed standard deviations. The range is left vacant in the last lines because the small N's make the sigmas unreliable.

one school will include an age range valving both with that school's scholarship standards, which vary geographically, and with the students' intelligence quotients, which vary according to social, economic and other conditions. More logically therefore, athletic standards should be referred to age. Observations were accordingly collected in a private school in California, the averages graduated mathematically by methods presented above and the resultant standards arranged in Table II for practical convenience of athletic coaches. The predicted values are stated at exact years and half-years (instead of at 0.25 yr and 0.75 yr, necessarily used in reducing the raw data). Expected performance at fractional ages can be interpolated or, if desired, computed from the formula. Besides the average there are also tabulated certain lower and upper borders which permit any particular boy to be assessed as either handicapped or superior.

The only age standards for sprinting-speed seem to be the Philadelphia "public school age aim charts," quoted by Bovard and Cozens¹¹ in 1930. In the 100 yard dash our private school boys were faster. By how much exactly we cannot say because we do not find in that reference whether age was recorded to nearest or to last birthday.

CONCLUSIONS

1 The rate of speed in running of which schoolboys are capable has been shown to be correlated with age and, hence, to be one of the phases of general growth which is susceptible to mathematical treatment like growth in size of the body as a whole and of its various organs, systems, and activities.

2 An analysis of the data for the 100-yard dash obtained from 992 tests of schoolboys from nine to twenty years of age shows that average speeds in seconds when calculated for and plotted against years of age form a symmetrical flattened S curve, such as is characteristic of several forms of growth. From this curve a mathematical formula has been computed, agreeing satisfactorily with the observations which in mathematical terminology is a logistic, and in physiologic terminology an autocatalytic, curve. The feature of this kind of growth is that the annual gains, instead of becoming smaller year by year as appears true of some traits, *increase* up to puberty and thereafter decrease, so that these gains plotted against age look like the bell shaped curve of probability. Speed in sprinting has, therefore, been shown to be an aspect of growth susceptible of fairly precise prediction.

3 A table of standards, based on the present rather large series of observations for the approximate period of late childhood and of adolescence is presented which may be of practical service to school physicians and athletic directors.

For mathematical advice we are greatly indebted to Dr. Holbrook Working.

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HEMORRHAGE AND SUBSEQUENT CALCIFICATION OF THE SUPRARENAL

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HEMORRHAGE in the suprarenal gland occurs relatively frequently in infants and children. There are a number of causes. This study was prompted by the clinical observation of a patient with massive suprarenal hemorrhage, in whom, at postmortem, calcification was found in the old blood clot.

In the newborn massive hemorrhage of the suprarenal has been described^{1, 9}. It is also seen in older children and adults^{7, 8, 10, 23}. The clinical course in the newborn has been described as follows: shock, listlessness, refusal of food, rapid respiration, rapidly developing anemia, distention, bogginess of the abdomen with or without bluish discoloration, and occasionally a palpable mass. Pyrexia was observed by some^{6, 7, 22}. Cures were reported by transfusions,⁵ hormone therapy,^{6, 23} and operation.² The etiology was given as (a) probably part of hemorrhagic disease of newborn, (b) difficult delivery (breech), (c) Schultz method of resuscitation, (d) increased pressure in the inferior vena cava and suprarenal vein^{5, 6, 7, 8}. Smaller hemorrhages which are probably incidental findings and not the primary cause of death are fairly frequent.

Severe sepsis causing suprarenal hemorrhage has been recorded^{7, 10, 17}. It may be due to thrombosis of suprarenal veins, emboli, or toxic damage to the gland. This seems to be the most frequent cause after the newborn period.

In patients with fatal burns, hemorrhage in the suprarenal is quite common^{8, 15, 19}.

Suprarenal apoplexy in adults is described and has nearly always been associated with an infection^{10, 11, 16, 17, 18}. Materna³² showed in some of the patients dying from suprarenal hemorrhage that there was an excess of adrenalin in the blood stream causing an adrenalin toxemia.

Calcification of the suprarenal glands has been observed in patients with Addison's disease²⁴⁻²⁷ in whom there has been tuberculosis of the suprarenal followed by insufficiency of the gland. Calcification is reported by a few authors as occurring in children^{25, 27, 29}. Adams and Nicolls³⁰ noted it in four patients over forty years of age in whom there was no tuberculosis, and they considered it may have followed a suprarenal hemorrhage at birth. Marine²⁸ reports calcification of

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the suprarenals in cats, usually following distemper. The symptoms were similar to insufficiency of the gland as observed in the animals surviving double suprarenalectomy for three weeks.

Banting and Gairns²¹ found in adrenalectomized dogs that injection of adrenalin free cortex prolonged life. Also they noted that Ringer's solution was more effective than any other intravenous solution.

The material for this study is derived from the records of forty-three infants and children in whom suprarenal hemorrhage was found at post mortem. These have been observed during the last fifteen years and the frequency is somewhat greater than was expected. Suprarenal hemorrhage was found forty-three times in 3,637 consecutive post mortems, an incidence of 1.19 per cent, fifteen occurred in newborn infants, and twenty-eight in older infants and children. The data may be found in Table I.

NEWBORN GROUP

Of the cases in this group only one was diagnosed clinically (Case 41). In this case labor was difficult, the infant suffered collapse, irregular respirations, and weak pulse. A mass was felt in the left flank. This patient was also suffering from intracranial hemorrhage and, in spite of repeated transfusions, died. Six of the fifteen were prematurely born infants, the type of labor was not recorded in the majority, but records of four showed difficult delivery (Cases 2, 7, 41, and 42). Ten of the fifteen were brought to the hospital under one week of age, and all died shortly after admission. In the postmortem examinations very few had uncomplicated suprarenal hemorrhage. Cases 2, 3, 7, 9, 10, 11, 13, and 42 showed the smallest number of associated conditions, and if one analyzes the clinical findings in these, the symptoms and signs divide into those of (a) collapse and (b) hyperirritability. On the one hand, there was collapse, cyanosis, irregular gasping respiration, weakness, listlessness, subnormal temperature, lack of suckling, and in some the unconfirmed clinical diagnoses of bronchopneumonia, sepsis, intracranial hemorrhage, and alimentary intoxication were made. The other clinical picture was one of twitching of the muscles, screaming, convulsions, and fever. The unconfirmed clinical diagnosis in these (Cases 7, 10, and 42) was intracranial hemorrhage. All the cases being considered, the symptoms and signs fall into these two divisions, but the other conditions from which the patient suffered may have been contributory.

In three patients (Cases 2, 41, 42—Figs 1 and 2) a mass was observed on palpation of the abdomen, though in the first it was thought to be liver. There were four instances in which the mass was large enough to have been easily palpable. In ten of the fifteen cases, the hemorrhage was sufficiently extensive to destroy the structure of one or both glands and so disorganize the parenchyma that it would not seem possible for the usual function to continue.

TABLE I

**Suprarenal Hemorrhages in Newborn Infants*

CASE NO	AGE ON ADMISSION	CLINICAL COURSE	CLINICAL DIAGNOSIS	ANATOMICAL FINDINGS	MICROSCOPIO FINDINGS
1 Male	2 wk	Child screamed 8 hr before admission, collapsed, died day after admission	Prematurity, peritonitis	Omphalitis, peritonitis, pulmonary edema. Small hemorrhages in both suprarenals. <i>Streptococcus mucosus cap sulatus</i> recovered from umbilicus and peritoneum	Small recent cortical and medullary hemorrhages
2 Male	3 days	Difficult resuscitation, failure to take food. Collapse, breathing and gasping irregularly. Liver enlarged. Fine crepitations in lung	Bronchopneumonia, septicemia	Massive right suprarenal hemorrhage size of a small orange. Peritoneal hemorrhage	No normal suprarenal tissue left. Cells widely separated by extensive hemorrhage
3 Female	4 days	Prematurity. Pimples on neonatorum, fever. Child given an oxysanguination transfusion and died shortly	Prematurity, septicemia, impotiga	Bilateral suprarenal hemorrhage — capsule distended with dark blood clot. Bronchopneumonia	Cortex and medulla disorganized by extensive recent hemorrhage
4 Female	17 hr	Premature baby with subnormal temperature, died shortly after admission	Prematurity	Atelectasis. Small hemorrhage into suprarenals, patent foramen ovale. Potechial hemorrhage into lungs, heart, and liver	
5 Male	1 day	Premature one day old baby admitted with a subnormal temperature, died shortly after admission	Prematurity, congenital heart disease	Pulmonary atelectasis, intracranial hemorrhage, bilateral hemorrhage in suprarenals (1 dram of blood clot in each). Patent ductus arteriosus and foramen ovale	
6 Male	3 wk	Discharging eyes since birth. Temperature rose very high after admission, to 108° F, and child died same day	Prematurity, ophthalmia neonatorum	Intracranial hemorrhage, bronchopneumonia, otitis media, bilateral suprarenal hemorrhage	Suprarenal gland disorganized by recent hemorrhage

*Cases 41 and 42 also are of the newborn group

TABLE I--Cont'd

			Twitching of limbs difficult labor Decompression was done. Nothing found baby died on table.	Cerebral hemorrhage.	Decompression wound of cranium. Few petechial hemorrhages in the cerebral cortex Hemorrhage into both suprarrenal from 1 to 2 drams of blood clot.	Only thin layer of suprarrenal cortex remained. Medulla filled with large blood clot.
7	Female	3 days				
8	Male	2 days	Vomiting and mucus in throat. Barium by mouth found in lung Child vomited while in hospital. Died in 2 days. No fever	Tracheoesophageal fistula.	Intracranial hemorrhage Bronchopneumonia Massive hemorrhage with destruction of suprarrenal.	Practically the whole parenchyma of the suprarrenal was destroyed. Large blood clot in medulla.
9	Male	12 hr	Immature infant 12 hours old died 24 hours after admits alone.	Prematurity	Atelectasis, patent ductus arteriosus and foramen ovale. Left suprarrenal small hemorrhage Right had 1 dram of blood	
10	Female	1 day	Screaming convulsions, and twitching of muscles, temperature 100 F Died in 1 day	Cerebral hemorrhage.	Pulmonary hemorrhage, suprarrenal hemorrhage right, 6 c.c. left petechial.	Right suprarrenal greatly disorganized by hemorrhage
11	Male	9 days	Vomiting blood weakness and pallor inability to nurse properly increasing since birth. Transfusion Died next day	Hemorrhage of newborn.	Hemorrhage (gastrointestinal tract, lungs, suprarrenal)	Suprarrenal tissue, with exception of thin zone of cortex destroyed by hemorrhage which had clotted and showed early organization and phagocytosis of hemosiderin.
12	Male	5 days	Taking feeding poorly since birth. Feeble cry Cyanosis one day Died day after admission	Intracranial hemorrhage, omphalitis.	Sepsis neonatorum (omphalitis) Septicemia Staphylococcus aureus Hemorrhage in suprarrenal.	Diffuse hemorrhage in suprarrenal not altering structure to any extent.
13	Female	10 days	Diarrhea for 48 hours, child admitted in collapse heart rapid Dehydrated and blue put in oxygen tent, and transfusion given. Died day of admission.	Alimentary intonation bronchitis	Recent hemorrhage disorganizing left suprarrenal.	

TABLE I—CONT'D
Infection as Probable Cause of Suprarenal Hemorrhage

CASE NO	AGE ON ADMISSION	CLINICAL COURSE	CLINICAL DIAGNOSIS	ANATOMICAL FINDINGS	MICROSCOPIC FINDINGS
14 Male	11 mo	Loss of appetite, cough, irritability, lethargy, difficult feeding problem. Died some days after admission.	Infectious intoxication, nasopharyngitis, otitis media	Chronic pyelonephritis. Suprarenal hemorrhage (small)	Small diffuse medullary hemorrhage showing phagocytosis of hemosiderin. No fibrosis or calcification.
15 Female	3½ mo	Diarrhea 4 days, vomiting 2 days. Drowsiness day of admission. No improvement, fever developed, petechial hemorrhages on chest. Died 20 days after admission.	Septicemia	Septicemia, hemorrhagic gastroenterocolitis. Suprarenal hemorrhage.	Recent diffuse hemorrhage into cortex of suprarenal. Congestion of medulla.
16 Male	5 mo	Loosing weight 7 weeks. Furolosis 4 days. Admitted as an atrophic infant with otitis media. Died 7 days after admission.	Decomposition, furunculosis, formentative diarrhea, otitis media	Bronchopneumonia, otitis media. Hemorrhage into left suprarenal, from ½ to 1 dram of blood.	Recent localized hemorrhage in to left suprarenal.
17 Male	3 yr	Cough and fever 7 weeks. Lost 2 days. Bronchopneumonia and septicemia, edema of cheek 2 days before death, petechial hemorrhages. Died 9 days after admission.	Bronchopneumonia, septicemia, otitis media	Septicemia, bronchopneumonia. Otitis media, cellulitis, suprarenal hemorrhage (right).	Recent diffuse hemorrhage into cortex and medulla of right suprarenal.
18 Female	14 mo	Vomiting 1 day. Diarrhea and rapid breathing, coughing. Came in moribund with temperature 105° F, and died.	Influenza, infectious intoxication	Blotchy red rash and petechial hemorrhages on trunk. Hemorrhage into suprarenals. Blood and lung cultures negative.	Recent, diffuse bilateral hemorrhage into cortex and medulla.

TABLE I--CONT'D

19 Female	8 mo	Child had alimentary intoxication 3 weeks before admission developed gangrene of buttocks and pneumonia died 2 days after admission.	Bronchopneumonia; septicaemia; gangrene of buttocks.	Thrombosis (internal and straight sinuses, cerebral veins inferior vena cava) Bronchopneumonia, septicaemia. Gangrene of buttocks. Suprarenal hemorrhage, right renal infarction.	Right suprarenal showed medulla filled with blood clot and cortex broken up by hemorrhage
20 Female	3 mo	Discharging nose 5 days, twitchy fever and vomiting 3 days. Drowsy and refusing food 1 day. Admitted in moribund condition. L.P. revealed purulent spinal fluid.	Meningitis (hemolytic streptococcus)	Purulent meningitis. Cong cystic kidney Hemorrhage into suprarenal. Septicaemia.	Modern to diffuse recent hemorrhage in medulla.
21 Female	4½ yr	Erysipelas for 10 days before entry. Mongolian idiosyncrasy. Erysipelas spread and child finally died.	Erysipelas, Vincent's angina, mongollism	Septicaemia, fibrinous pleurisy Purulent peritonitis, serofibrinous peritonitis, necrotic nephritis. Mongollism. Suprarenal hemorrhage	Small recent diffuse hemorrhage in medulla and cortex.
22 Female	12 mo	Cough, loose stools drowsy 3 months. Admitted with acute upper respiratory infection, developed bronchopneumonia and pyelonephritis, died 10 days after admission.	Pyelitis, bronchopneumonia.	Otitis media. Mastoiditis, bronchopneumonia. Pyelonephritis. Recent left suprarenal hemorrhage (½ dram)	
23 Male	9 yr	Came in with loss of appetite, fever, vomiting, loss of consciousness. Was convulsive and dehydrated with high fever. Died a few hours after admission.	Bilateral otitis media, nasopharyngitis, infectious intoxication.	Generalized thrombosis of cerebral veins. Acute encephalitis with softening of basal ganglia. Double otitis media and mastoiditis. Hemorrhage into right suprarenal.	Thrombosis of right suprarenal vein and recent cortical hemorrhage.

TABLE I—CONT'D
Infection as Probable Cause of Suprarenal Hemorrhage

CASE NO	AGE ON ADMISSION	CLINICAL COURSE	CLINICAL DIAGNOSIS	ANATOMICAL FINDINGS	MICROSCOPIC FINDINGS
24 Male	28 days	Premature baby developed a cold, vomiting, diarrhea and loose stools, died 3 days after admission.	Prematurity, infectious intoxication	Bronchopneumonia, pleurisy, otitis media, bilateral suprarenal hemorrhage, marked in left	
25 Female	5 wk	Head cold, irritability, drowsiness, vomiting, died in admitting room	Intestinal intoxication, meningococcus septicemia	Meningococcus septicemia Generalized peritonitis, bilateral pleural effusion, septic pneumonia Petechial hemorrhages in skin, bilateral suprarenal hemorrhage	The whole gland was disorganized by extensive diffuse hemorrhage
26 Female	9 yr	Fever, drowsiness, vomiting 17 hours Delirium and purple blotches 3 or 4 hours Child died shortly after admission with fulminating cerebrospinal meningitis	Meningococcus meningitis, meningococcus septicemia	Meningococcus septicemia and meningitis Petechial suprarenal hemorrhages Purpuric spots on skin	Foci of hemorrhage throughout the suprarenals
27 Male	7 mo	Child had summer diarrhea for 5 wk before admission. On admission was toxic and dehydrated, running septic type of fever Transfusion and treatment for alimentary intoxication given. Developed bronchopneumonia and died	Acute intestinal intoxication Bronchopneumonia	Hemorrhage into left suprarenal Bronchopneumonia	Recent left medullary hemorrhage
28 Male	5 mo	This child had fulminating meningococcus meningitis, was well until 16 hours before admission Died 1 hour later	Meningococcus meningitis	Meningococcus septicemia and meningitis Purpura Bronchopneumonia Massive suprarenal hemorrhage	Whole gland disorganized by hemorrhage Here and there scattered strands of adrenal tissue otherwise nearly all blood clot

TABLE I—Cont'd

Burns as Cause of Suprarenal Hemorrhage

29 Female	3 1/2 yr	Burned and scalded condition of shock on admission Area of buttocks and thighs involved. This was tanned. Transfusion given Day after child looked well pulses 148 - 2 days later vomited blood, pulse 200 very listless and toxic Died very suddenly	2nd and 3rd degree burns.	Burns. Duodenal ulcer with hemorrhage Bilateral supra renal hemorrhage	Eight suprarenal had an exten sive diffuse hemorrhage with some disorganization of tis sue The veins were throm bosed Left showed extensive hemorrhage and destruction of the whole gland with hem orrhage into surrounding tis sue
30 Female	3 1/2 yr	Burns on abdomen and but tocks Was quite toxic day after admission Later imid n convulsion and died	Burns, toxemia	Burns. No gross hemorrhage of the suprarenal.	Suprarenal hemorrhage in volving whole medulla of one gland
31 Female	3 1/2 yr	Admitted shortly after exten sive burns of the trunk Very restless collapsed while area was being cleaned Circula tion always poor Pulse not perceptible at wrists. B.P. 40 after adrenalin rose to 60 Child died of circula tory failure 15 hours after admission.	Burns.	Burns. Small suprarenal hem orrhage left. Peterkin hem orrhage in brain and myo cardium	
32 Female	9 yr	Scalded with water Child was toxic emaciated and definitely ill	Burns, toxemia sepsis.	Burns. Duodenal ulcer Gastric ulcers. Diffuse hemorrhage into suprarenal.	Extensive diffuse hemorrhage in both suprarenal glands with destruction of tissue

Miscellaneous Causes of Suprarenal Hemorrhages

33 Male	7 yr	Child was injured in automo bile accident B.P. unvaried 100 110 systolic. Pulse be came very rapid Decon pression done. Child died	Cerebral concussion Fracture of skull	Fracture of skull Infection of brain cerebral hemorrhage petechial Decompres sion wound. Suprarenal hem orrhage right	Considerable hemorrhage at one side of gland. Other portion appeared normal
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TABLE I—CONT'D

CASE NO	AGE ON ADMISSION	CLINICAL COURSE	CLINICAL DIAGNOSIS	ANATOMICAL FINDINGS	MICROSCOPIIC FINDINGS
34 Male	3½ mo	Child, group II, transfusion from a universal donor (1919) Child became blue, collapsed, passed bloody urine	Decomposition Anaphylaxis following transfusion	Petechial hemorrhages in lung Hemoglobinuria Serum fluid was blood stained Hemorrhages into suprarenals	Extensive diffuse hemorrhage into both cortex and medulla
<i>Sequelae of Suprarenal Hemorrhage</i>					
35 Male	3 mo	Child showed irritability, crying, twitching, vomiting 2 days Convulsion 1 day Tronseau's sign positive Died shortly after admission.	Rickets, tetany	Suprarenals large, ½ size of kidney Rickets Otitis media	Old hemorrhage, chiefly medullary, with organization, phagocytosis of hemosiderin
36 Male	5½ mo	Breech delivery, difficult Hematoma of buttocks, depressed fracture Difficult resuscitation High rasping cry for 2 wk, always been difficult to feed Some bending of ribs Developed otitis media, mastoiditis Developed diarrhea and died	Nasopharyngitis, double otitis media, mastoiditis, infectious intoxication	Mastoiditis, otitis media. Bronchopneumonia Purulent meningitis Calcareous deposits in suprarenal (micro)	Suprarenals showed large phagocytic cells containing blood pigment There were numerous areas of calcareous deposit
37 Male	4½ mo	B W, 8 pounds, normal labor Always difficult to feed Listless, developed an infection 3 days before admission and died following day Compliant vomiting, rapid respirations, and drowsiness	General peritonitis, septicemia	Peritonitis, septicemia, bronchopneumonia Calcification of right suprarenal	Right gland was larger than normal Cortex appeared normal, medulla entirely replaced by calcareous deposits, fibrous tissue, and phagocytic cells filled with hemosiderin

TABLE I--Cont'd

38 Male	9½ mo	Screaming fits, frequently anorexia 4 wk., developed bronchitis, had pus in urine on admission. <i>B. coli</i> cultured from urine. X ray picture of abdomen showed calcareous shadows in region of kidney but were thought to be renal calculi. Child developed bronchopneumonia and died.	Pyelitis, bronchopneumonia, otitis media, ventral hernia	Otitis media and mastoiditis. Bronchopneumonia. Calcareous deposits in right suprarenal, in gross, feeling as if stones were present.	Left gland showed veins thrombosed in medulla with some calcareous changes and recanalization. Right contained many calcareous deposits and phagocytic cells with hemosiderin. Medulla all destroyed. Cortex only a thin shell.
39 Female	7 mo	Recurrent attacks of irritability, fever, pallor, failure to gain, vomiting 4 mo. Normal labor. Admitted with nasopharyngitis, otitis media and pyelonephritis. Child developed diarrhea and died 1 mo after admission. X ray pictures of abdomen showed irregular calcified areas in region of suprarenals.	Chronic pyelitis, otitis media, anemia, nasopharyngitis.	Otitis media, mastoiditis, subacute pyelonephritis. Thrombosis of inferior vena cava. Splenomegaly, calcification of both suprarenals.	Medulla and part of cortex had been replaced by calcareous deposits. In one there was the formation of osseous tissue with bone marrow. Hemosiderin was present in some of the phagocytic cells.
40 Male	17 mo	Always feeding problem. Admitted with vomiting, convulsions, and drowsiness. Child was drowsy and had a peculiar irritable cry. Collapsed shortly after admission and died.	Tuberculous meningitis (not confirmed)	Calcareous deposits in both suprarenals. (No evidence of tuberculous found in post mortem.)	Cortical cells normal, but structure altered by large old medullary hemorrhage showing hemosiderin and calcification.
41 Male	7 days	Breech delivery, forceps, difficult resuscitation. Irregular shallow breathing. Not moving right side of body. Mass appeared under the chin. Mass felt in abdomen; child pale. Transfusion no recovery. Died three days later.	Hemorrhage of newborn. Left suprarenal hemorrhage. Hematoma of right cervical region.	Intraorbital hemorrhage, subarachnoid. Multiple small lung hemorrhages. Massive suprarenal hemorrhage left, small suprarenal hemorrhage right. Hematoma in cervical region.	Right showed marked diffuse hemorrhage with calcareous deposits. Left completely destroyed and replaced by blood clot.

TABLE I—CONT'D

<i>Sequelae of Supratentorial Hemorrhage</i>				
CASE NO	AGE ON ADMISSION	CLINICAL COURSE	CLINICAL DIAGNOSIS	ANATOMICAL FINDINGS
42 Female	6 days	Prolonged instrumental labor, pallor, listlessness, collapse, low temperature for 24 hours. Evidence of free fluid in abdomen. Hg 35 per cent. Transfusion. Masses felt in abdomen on both sides, in kidney region. Twitching began. Admission temperature, 95° F., came up after transfusion. Died 36 hr after admission.	Hemorrhage of newborn. Intracranial hemorrhage, cerebellar hemorrhage.	Right supratentorial hemorrhage. Bilateral massive supratentorial hemorrhage.
43 Male	5½ yr	Inability to walk, 3½ mo. Tremor of hands and arms, tiring easily. Began to have difficulty in talking. Recently had incontinence of urine and feces. PE revealed a weak child. Marked choking of the disks. Reflexes variable.	Midline cerebellar tumor.	Right supratentorial fibrosed. Very little gland tissue remaining. In the center of the fibrous tissue were calcareous deposits and bone formation with marrow spaces. Adjacent to this there was phagocytosis of hemosiderin.



Fig. 1.—Photographs of massive suprarenal hemorrhage. *A* and *C* (Cases 41 and 42, respectively) were from the newborn group. *B* (Case 29) shows the result of a burn. Note the large size of hemorrhage in *A* (Case 41).



Fig. 2.—Case 41. Photographs showing all the viscera and the relation of hematomas, the large one on the left and smaller one on the right. *A* Anterior view *B* Posterior view. 1 Lungs 2 heart 3 diaphragm 4 stomach 5 spleen 6 mass 7 transverse colon 8 small bowel 9 liver 10 right suprarenal blood clot 11 right kidney 12 small bowel 13 perirenal fat.

Suprarenal hemorrhage was associated with definite hemorrhagic disease of the newborn in one case only (Case 1). Intracranial hemorrhage was present in five cases, indicating that the delivery was probably difficult. Sepsis or bronchopneumonia occurred in five and may have been a factor in the production of the hemorrhage.

OLDER AGE GROUP

Infection—In the group of the older infants and children with infection as the probable cause of the hemorrhage in the suprarenal, there was only one (Case 18) in which the infection could possibly be excluded as the cause of the symptoms. In this patient the onset was twenty-four hours before admission with vomiting. Diarrhea followed with rapid respirations and high fever, the child was moribund on admission. A blotchy rash and petechial hemorrhages were noted. The pathologic findings were negative except for the hemorrhage. There was no discoverable infection in this patient, although the fever of 105° F. made it seem probable. It is possible that this may have been a fulminating cerebrospinal meningitis.

Five of the fifteen patients had lesions in the kidney, such as pyelonephritis, hydronephrosis, and acute nephritis. Six showed involvement of the brain, either in the form of meningitis or thrombosis of the cerebral veins. Septicemia was present in seven. Bronchopneumonia was found in seven, of which three were associated with generalized sepsis. The hemorrhage in six of the fifteen patients was extensive enough to disorganize the gland somewhat, but in the majority consisted of diffuse extravasation of blood. Organized blood clot with phagocytosis was present in one case.

Burns—In the four patients with suprarenal hemorrhage resulting from severe burns, the symptoms were those of collapse and circulatory failure. This may be due to the toxemia from the burn, or possibly the suprarenal hemorrhage may have produced these symptoms. Two had associated duodenal ulcers. Microscopically, the affected suprarenal glands were found practically destroyed by the hemorrhage (Fig. 1).

Miscellaneous Causes—In the miscellaneous group of two cases, the first was the result of an automobile accident, death was probably due to the fractured skull. However, in the clinical course it is interesting that, in spite of the cranial and cerebral damage, the pulse became rapid and blood pressure remained low. Increased intracranial pressure usually causes the opposite effect.

The other case occurred as a result of a transfusion in which a so called universal donor was used. The child collapsed, became blue, and died. This course may have been due to the suprarenal hemorrhage or possibly as a result of the many other changes occurring from incompatibility of the blood. Following this catastrophe, the practice of using

universal donors was discontinued in this hospital. There were no cases of suprarenal hemorrhage as a sequence to incompatibility of donors' blood in the literature at our disposal.

Sequelae.—In one patient there was fibrosis of the suprarenal gland following a former hemorrhage that was becoming organized. Calcification of the suprarenal was not diagnosed antemortem in any of the eight patients in whom it was found at autopsy (Figs. 3 and 4). In two (Cases 38 and 39), however, there were roentgenograms taken during life which



Fig. 3.—Roentgenogram of abdomen showing calcification in region of suprarenal (Case 39).

showed unusual opacities on both sides of the vertebral column (Fig. 3). These were subsequently shown to be the calcified suprarenal glands (Fig. 4). In Cases 36, 41, and 42 there was difficult delivery and history suggestive of suprarenal hemorrhage occurring at birth. In Cases 38 and 39 there was a chronic kidney disease, pyelonephritis.

In all the cases showing calcification, with the exception of Case 40, along with the calcareous deposits, there was evidence of previous hemorrhage in the form of hemosiderin contained within phagocytic cells. In

Cases 41 and 42 there is no doubt that the calcareous deposit was the result of the hemorrhage, and in five of the remaining six cases it is practically certain

How much the change in the suprarenal gland had affected these patients, six of whom lived beyond the newborn period, is hard to say. However, in the history of each it is evident that they had not been normal children. "They have always been a feeding problem," "listless," etc.

DISCUSSION

The suprarenal glands develop in two parts^{33, 34}. The cortex comes from the ectodermic epithelium over the mesonephros and includes part of the mesonephric tubules. The medulla arises from part of the neural ridge which goes to form the sympathetic nervous system. The cortex

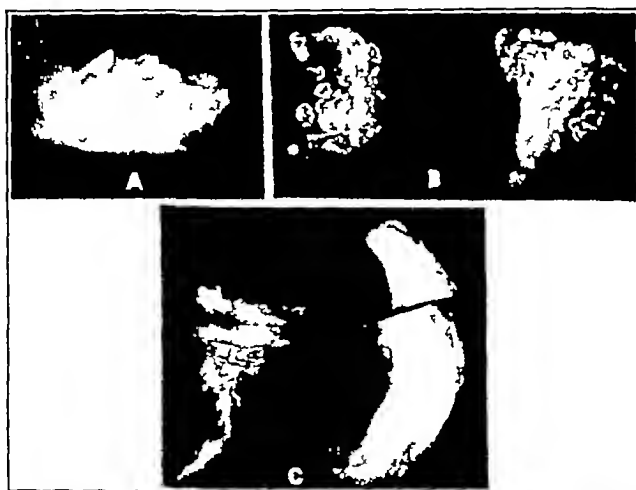


Fig 4—Roentgenograms of calcification in suprarenal taken after removal at post-mortem. A, Case 38. B, Case 39. C, Case 43.

is yellowish in color, and the medulla, reddish brown. The glands are situated on the upper pole of either kidney. Accessory suprarenal glands are frequently found in the broad ligament of the female or the epididymis of the male. They are endocrine glands which are necessary for life³⁵. The animal can live without the medulla, but the cortex is indispensable. Both parts are capable of regeneration. The suprarenal gland is the most vascular organ of the body in that it receives the greatest relative amount of blood for its weight every minute. The blood supply comes from branches of the inferior phrenic, aorta, and renal arteries.

In the newborn the medulla is relatively small, and the cortex is quite large and loose. In the first two weeks of life the central portion of the cortex becomes quite vascular, and the medulla grows at the expense of this portion.

In our series agreeing with others, hemorrhage of the suprarenal gland in the newborn is usually found during the first week of life. This is during the period of hemorrhagic disease of the newborn which may be an etiologic factor. The other factors to be kept in mind during this period are damage during labor and the increased vascularity occurring in the neonatal period.

During the later period in which infection is a factor, most writers indicate that a blood stream infection is present. Attention has not hitherto been drawn to the nearby involvement of the kidney with pyelonephritis which probably spreads to the suprarenal gland by direct extension or by way of the veins in thrombophlebitis. (This was present in Cases 23 and 38.) Chronic kidney disease was present in five



FIG. 5



FIG. 6

FIG. 5.—Case 41. Patient ten days old. Calcification has already taken place immediately underneath the cortex, adjacent to the hemorrhage. A similar picture was seen in Case 42 (patient 8 days old). H. & E. $\times 120$.

FIG. 6.—Case 38. Patient 9½ months old. In lower part of field can be seen organized blood clot, while above this are deposits of calcium. H. & E. $\times 110$.

with hemorrhage alone and in three with calcification, or 31 per cent of the patients beyond the newborn period.

Fifty per cent of the infection group had septicemia. Many of these had involvement of meninges as well. Three of these were fulminating cases of meningococcus septicemia and Case 18 may have been. In a few bronchopneumonia and upper respiratory infection were all that could be found.

Calcification of the suprarenal is usually thought of as a late event in Addison's disease or tuberculosis of the suprarenal gland. However it was described by Marine²⁶ in cats suffering from distemper, and

reference to the possibility of its occurring as a result of suprarenal hemorrhage in the newborn was made by Adams and Nicolls³⁰ and Mallory³¹. Again some state that it may be the result of necrosis of the gland. In this series it definitely followed previous hemorrhage.

When one recalls the ease with which calcium salts are deposited elsewhere in the body, then deposition in old adrenal hemorrhages is not surprising. One common type for such calcareous change is in old thrombi. The constituents of a thrombus and a localized hemorrhage are quite similar. Both may undergo organization and frequently show phagocytosis of blood pigment and occasionally calcification. As a matter of fact, Case 39 showed, in addition to the adrenal lesion, a recent thrombus in the inferior vena cava with calcareous degeneration. This,



Fig 7



Fig 8

Fig 7—Case 37. Patient 4½ mo. old. A small amount of cortex can be seen on either side of the medulla which is almost entirely replaced by calcium. H. & E. $\times 100$.

Fig 8—Case 37. Patient 4½ mo. old. Phagocytic cells in medulla, packed with hemosiderin. H. & E. $\times 140$.

however, had obviously developed much more recently than that in the adrenals.

The time required for calcium to be deposited is also a matter of interest. The youngest patient in the series showing calcification was only eight days old (Case 42). In this instance the hemorrhage into and around the right suprarenal was very extensive while less marked hemorrhage had occurred in the left gland. However, at this early date, calcareous deposits could already be seen lying just at the edge of the blood clot immediately underneath the remains of the thinned-out cortex. Similar calcareous deposits also immediately underneath the cortex were found in Case 41. This infant died at the age of ten days.

That this degree of calcification can take place in the short space of eight to ten days is not at all surprising in the light of what is known regarding the calcification of a callus surrounding a fracture. Here, also, the calcification is preceded by hemorrhage, and while such calcification in the adult may not be recognized roentgenologically for a matter of nearly four weeks in children it may take place as early as the end of one week,³⁰ and, according to Rolph,³¹ the younger the infant, the more rapidly calcification occurs. Case 41 is also of interest because of the extensive calcareous deposits in the tubules of the cortex of both kidneys (Fig 5). These deposits, however, are on the whole more dense and tend to be concentrically arranged within the tubules the epithelial cells of which seem to have disappeared. Whether they are in any way



FIG 9



FIG 10

Fig 9.—Case 10. Patient 17 mo. old. Here the calcareous material in the medulla approaches the capsule of the gland. A segment of the cortex is also almost completely destroyed. H & E. $\times 120$.

Fig. 10.—Case 39. Patient 7 mo. old. Extensive replacement of both cortex and medulla with calcareous material, showing bony metaplasia in the center of the field. A similar picture was seen in Case 43. H & E. $\times 125$.

related to the suprarenal hemorrhage or whether they are even entirely of postnatal development is a matter of speculation.

Other evidences of changes taking place in the clot are also seen at an early date. In a nine-day old infant (Case 11) with fairly marked bilateral suprarenal hemorrhage, while no calcification was seen in either gland, there was already considerable fibroblastic proliferation in the periphery of the clot where it lay in contact with the thin layer of cortical cells immediately underneath the capsule. Many of the red cells by this time had also undergone varying degrees of disintegration, in some places forming a more or less homogeneous pink staining mass. Phagocytosis of blood pigment was not noticed in any of the cases as early as this.

In those children surviving for several months, evidence of hemorrhage could still be seen in the marked irregularity of the structure of the gland and by the presence of fibrosis, phagocytosis or iron-containing pigment, and by irregular deposits of calcium (Fig 6—9½ mo, Figs 7 and 8—4¾ mo, Fig 9—17 mo). In Cases 39 and 43, in addition to the calcification, there was also bony metaplasia with formation of marrow spaces (Fig 10). Such metaplasia has long been recognized as occurring in the sclerotic walls of blood vessels in degenerated tumors, as for example, in the uterus and the thyroid, and we have seen one such instance in a case of an ependymoma of the brain in a child. In these instances it must be assumed that some of the connective tissue cells in the region of the calcareous deposits become specialized as osteoblasts, thus giving rise in the process of time to true bone.

Total loss of the suprarenal is incompatible with life. From this series it is evident that there is partial damage to the gland which is not fatal at the time. This is quite evident from the patients with calcification as the hemorrhage must have occurred some time previously. Some of these were not in good health previous to the final illness. It is possible that partial damage may modify the life and metabolism of the individual, this possibility is interesting.

SUMMARY

The records of forty-three cases of suprarenal hemorrhage observed at postmortem have been discussed. Only one case was diagnosed clinically.

Fifteen of these were in newborn infants. The symptoms noted in this group were of two types—on the one hand, collapse, on the other, stimulation.

In the older age group fifteen cases of suprarenal hemorrhage were found associated with infection. Chronic renal disease, septicemia, and meningitis were the most frequently associated infections.

Four patients with burns, one following a severe accident, and one a transfusion from an incompatible donor made up the miscellaneous group.

In seven cases in which death was due to intercurrent disease, calcification was found in six cases and fibrosis in one. In two patients in the newborn period with fatal massive hemorrhage of the suprarenal, beginning calcification was found microscopically. In eight of the newborns there was definite evidence of previous hemorrhage into the gland. Some of these patients had shown, prior to the final illness, a tendency to be less robust than normal infants of the same age.

A résumé of the available literature is given.

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CHOREA IS IT A MANIFESTATION OF RHEUMATIC FEVER?

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SEVEN years ago we began a study of chorea and its relation to rheumatic infection in childhood. Provisions were made for the study by grouping all hospital and dispensary patients with chorea into a special clinic. Up to date approximately 150 patients have been registered, a number presenting an unusual opportunity for study. Originally we had no doubt as to the rheumatic origin of chorea, but as the study progressed we have come to question the absolute accuracy of this orthodox concept.

PLAN OF STUDY

Four methods of approach were employed

1 A careful detailed social service survey of fifty-eight of these patients †

2 A review of all their hospital and clinical records

3 A comparison with a control group‡. One of us spent six weeks in a camp especially designed to provide convalescent care for children, aged from seven to fifteen years, suffering with rheumatic heart disease. This group, offering a somewhat similar social background to our chorea group, was used as a control to determine the frequency of a history of chorea in rheumatic endocarditis.

4 A final physical reexamination of forty-five patients with special reference to cardiac findings, including fluoroscopy and electrocardiography. In these forty-five both hospital and clinic records were especially satisfactory. This group was chosen to give a cross-section of the larger material.

LITERATURE

It is not our purpose to review in detail the voluminous literature but simply to call attention to the trends since we started our investi-

From the Sarah Morris Hospital for Children and the children's cardiac service of the Mandel Clinic of Michael Reese Hospital aided by the Emil and Fanny Wedeles Fund for the Study of Diseases of the Heart and Circulation.

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gations. In 1927 one of us¹ noted that tonsillectomy had no appreciable effect upon the course of chorea and tentatively raised the question as to whether all chorea was rheumatic in origin. The same year Kaiser² also noted that tonsillectomy had no effect upon the course of chorea but that the tonsillectomized patients were less likely to develop endocarditis. These conclusions were corroborated in his later studies.³ Apparently Kaiser accepted chorea as a manifestation of a rheumatic infection. Working independently we⁴ arrived at conclusions similar to Kaiser's but reiterated our question as to the rheumatic origin of all instances of chorea.

These studies have had little effect upon the subsequent literature. The majority of observers still accept chorea as a manifestation of a rheumatic infection or, at any rate, of a chronic streptococcus infection. For example, only recently Luth and Sutton⁵ have reported cases of chorea occurring in the negro, which they apparently accept as a rheumatic manifestation. Occasionally authors have attempted to relate chorea to other origins, such as encephalitis,⁶ metabolic or constitutional factors,⁷ or derangements of the thyroid, parathyroid or adrenal glands.⁸ The effect of emotion has long been known and recently has been reemphasized by Sturton⁹ and Berg.¹⁰ In only one instance has the disease been studied as a behavior problem,¹¹ an approach we have found exceedingly beneficial in our plan of therapy.

Some recent experimental work has suggested differences between active rheumatic infection and chorea. Hassler and Mollor¹² report the sedimentation of red cells normal in chorea but definitely changed in active rheumatic infection. This has been corroborated in a recent paper by Elghammer.¹³

RESULTS

As a result of our own investigations our conception of the true nature of chorea has been altered. It now seems to us that chorea is a clinical syndrome rather than a disease entity, developing in a child, predisposed to it by heredity and constitution, upon exposure to exhausting psychic stimulation or various infectious factors. While some of the patients have suffered from rheumatic infection, the intimate relation of the rheumatic "virus" to the active etiology of chorea is by no means clear. Indeed, psychic trauma seems a far more important factor in its etiology than does any type of infection.

From the standpoint of etiology, the results of our statistical and clinical investigations are presented in composite in two groups, predisposing and active causes of the disease.

A. Predisposing Causes

Heredity.—Heart disease was reported in thirteen families but was mostly of the degenerative rather than the rheumatic type. These families gave no special history of rheumatic fever. A history of

chorea was obtained in fourteen families and of epilepsy and psychoneuroses in eight others. There were fourteen individuals in the families with thyroid disease. Every family with the exception of three was reported as poorly integrated from the social point of view with exaggerated emotional reactions.

Age—The onset of chorea occurred between the ages of five and thirteen years, most commonly between the ages of seven and twelve. No case of chorea occurred after puberty. All of the 150 cases recovered at or before this period, and there were no recurrences. In other words, something connected with the endocrine hormones seems to play a rôle—if not active, at any rate decidedly predisposing.

Sex—Twenty-nine patients were girls, and sixteen were boys.

Living Conditions—It is known that chorea like rheumatic fever occurs more frequently in the clinic than in wealthier private practice. In our series the wretchedness of living conditions seemed worse than in the usual clinic family. In one instance ten adults occupied four rooms. In twelve families, three or more persons occupied each room, and in thirty families the child shared his bed with another child or adult. The afflicted child was usually found sleeping in the dining room or kitchen, disturbed by the adults and kept awake by the lights, confusion, and blare of radios in adjacent tenements. Associated with poverty invariably is the question of food. While we have not quantitated the diets, it would appear that the diets were generally inadequate, especially as regards vegetables and fruits.

Temperament—It is known that chorea occurs chiefly in the intelligent overstimulated child. Thirty-eight of our forty-five children showed more than average intelligence in school. Five were definitely subnormal*. Chorea seems to occur most frequently in the child of a certain type—the one with introvertive tendencies. Practically all our children were found to be worrying about poverty and family problems, and all but three were considered poorly adjusted to the

TABLE I
SIZE OF FAMILY (58 PATIENTS)

NUMBER OF CHILDREN IN FAMILY	NUMBER OF PATIENTS
1	4
2	10
3	14
4	11
5	8
6	4
7	4
8	2
9	--
10	--
11	--
12	1

*These represent all the subnormal of the entire 150. Their records were included in the forty-five because they had all been hospitalized.

conditions at home or school. Twenty nine presented some definite behavior problem, severe enough to attract the attention of the school teacher. Of course, this may have been associated with the onset of the disease but if so, the onset is of a nature far more chronic and unusual than that of any common infection. In short, children with chorea seem to have a certain predisposing constitution which we have come to consider 'the chorea temperament'.

TABLE II
NUMERICAL STATUS IN FAMILY (38 PATIENTS)

ORDER OF BIRTH	PATIENTS
1st	20
2nd	13
3rd	10
4th	6
5th	3
6th	3
7th	1
8th	1
9th	--
10th	--
11th	--
12th	1

Regrouping Tables I and II as to oldest, youngest and only child shows

First born	20
Youngest	15
Only	6

Forty-one of fifty-eight children who developed chorea occupied positions in the family known to pediatricians and students of behavior as being hazardous.

B. Active Causes

We found nothing in the survey of the records, the searching social or medical investigations, or the final physical examination to suggest a close etiologic relationship of rheumatic fever or any specific infection to chorea. This is based on the following observations.

Onset—The onset is usually insidious, the child being nervous, irritable, and abnormal for weeks or months before the acute manifestations—very different from the history of ordinary infection. Sixty five per cent of our cases gave a history of symptoms long before the onset of the chorea and in only three did the chorea start acutely in an apparently stable individual.

Relation to Infection—Four children had suffered from scarlet fever and one from diphtheria. Six had definite clear cut articular rheumatism. Ten histories of vague aches and pains suggested rheumatic diathesis. In none did the chorea immediately follow the infection.

Clinical Course—There is nothing in the clinical course, temperature, pulse, or blood count to suggest acute infection

Cardiac Involvement—Thirteen children showed no cardiac findings at any time. In thirty-two there were some abnormal cardiac findings present at or during their period of hospitalization. Of these thirty-two, nineteen occurred in children with chorea but with no history of acute rheumatic fever. In these nineteen, the murmurs were transient and disappeared before the child left the hospital, very different from true rheumatic endocarditis. Of the thirteen in whom a murmur was present upon discharge from the hospital, nine showed some cardiac enlargement, but these findings had been present upon admission and the child had previously suffered from definite rheumatic infection. Most of these had tonsils. This will be discussed again later.

Psychic Factors—While our search offered no confirmation of the rheumatic etiology of chorea it did emphasize strikingly the importance of emotional factors in our clinical material. Psychic trauma seemed so intimately related to the actual onset in twenty-two cases as to force the question of its being the activating factor. Domestic discord was a prominent feature. It was plainly apparent in thirty-two families and extreme in thirteen. The onset of acute manifestations often followed a domestic crisis, such as divorce, separation, desertion, drunkenness, and the advent of stepbrothers and stepsisters. Other types of emotional injury were common. In three girls the onset was related to attempted rape. In four others the child lived in continuous dread of assault by undesirable characters in the neighborhood. One child was aware of the illicit sexual relations of her mother. In others the onset followed acute fright. In short, in our series psychic trauma resulting from fright or overwhelming grief stood out far more strikingly than did any history of infection.

Relation of Rheumatic Fever and Tonsils to Endocarditis—The final physical examination of our forty-five children showed a surprisingly low incidence of endocarditis compared to what we had expected to find. It also revealed an interesting relationship of this endocarditis to rheumatic fever and to the presence of tonsils as shown in Table III. Our findings confirm the previous observations that tonsillectomy has no effect upon the course, severity, duration, or tendency toward recurrence of chorea. Tonsillectomy does have a definite influence upon the development of endocarditis in patients who subsequently develop chorea.

The incidence of endocarditis in those choreic patients who still had tonsils and who gave a history of rheumatic arthritis is shown in the column on the left in Table III. It will be seen that practically all these patients developed endocarditis. In the middle columns are those patients with a questionable history of rheumatism, such as the

usual vague muscle aches and pains. In this group endocarditis occurred chiefly among those choreic patients who still retained their tonsils. On the right are the choreic patients with no history of rheumatic fever. Endocarditis again developed practically exclusively in those still retaining their tonsils. The absence of endocarditis in the large group of choreic patients with previous tonsillectomy and with no history of rheumatic fever is striking. Table III suggests definitely that in chorea endocarditis develops not as a result of the chorea but from a more or less independent tonsillar and rheumatic infection.

TABLE III
ENDOCARDITIS DEVELOPED IN OUR CHOREA CASES AS FOLLOWS

HISTORY OF RHEUMATISM AND TONSILS PRESENT WHEN BEEN	NO HISTORY OF RHEUMATISM, NO TONSILS	QUESTIONABLE HISTORY OF RHEUMATISM TONSILS PRESENT	QUESTIONABLE HISTORY OF RHEUMATISM NO TONSILS	NO HISTORY OF RHEUMATISM TONSILS PRESENT	NO HISTORY OF RHEUMATISM, NO TONSILS
++0	No cases	0++	000	0+	00
+ (youngest of 12)		+(1) 00	0+(1)	0+(1)	00
+(scarlet)		++0		000	00
+				00+(1)	00
				+	0+
					00
					00

CONTROL STUDY

An effort was made to compare the home conditions of this group with that of another group of clinic patients attending a special cardiac camp. In our group we had endeavored to determine how frequently chorea led to endocarditis. In the control group, all of whom had endocarditis we endeavored to determine how frequently a history of a preceding chorea could be elicited.

The social surveys were made by different workers and from different viewpoints hence we do not feel the comparison above criticism but there is certainly not the same history of marked poverty and domestic infelicity in the group of cardiacs. The medical histories of these control cardiac children are striking. Apparently uncomplicated chorea was only occasionally associated with the development of endocarditis. Of fifty five boys, forty one gave a history of rheumatic fever alone. Thirteen had rheumatic fever and chorea. Only one had chorea alone and here the cardiac lesion was doubtful. The girls were particularly interesting. Of ninety four, sixty eight gave a history of rheumatic fever alone, eighteen of rheumatic fever associated with chorea and eight of chorea alone. In four of the latter the cardiac lesion was doubtful. The incidence of chorea is twice as great in girls as in boys. Hence one would expect to find a history of

chorea more frequently in cardiac girls than boys. In this series chorea appeared in approximately the same percentage in either sex, and endocarditis only rarely followed uncomplicated chorea.

DISCUSSION

Until the infectious origin of chorea is either proved or repudiated no definite conclusions can be drawn as to etiology. To formulate our own opinions even after these seven years is still a difficult task. The clinic children with chorea come from an environment which seems to favor rheumatic infection. The two conditions do exist as concomitants and, when chorea is associated with a rheumatic infection, the subsequent endocarditis is often more severe. Furthermore, it seems to us that the constitution, diathesis, or temperament, and possibly the endocrine balance may play a predisposing rôle in *both* conditions though the introvertive tendencies seem universally present in the choreic children only. In the choreic patients, adverse social and economic conditions are an important contributing factor in producing a state of mental overstimulation. Given such a background, our histories suggest that any trauma, be it psychic or infectious, may precipitate an attack of chorea. As these children come from an environment favoring rheumatic infection and may themselves be constitutionally predisposed to rheumatic fever, it seems logical that such infection should frequently be listed in the etiology of chorea. On the other hand, observation of these children over a period of years and the finding that endocarditis is by no means an invariable complication of chorea, but almost exclusively a sequel of true rheumatic and tonsillar infection, lead us to think of rheumatic fever and chorea not as cause and effect but as concomitants in the same type of child. We feel that rheumatic infection is not a specific etiologic factor but one of the many, either psychic or infectious, which may precipitate the disease.

It is well known but perhaps insufficiently emphasized that these children never show any clinical sign of permanent organic defect of the nervous system. There is complete clinical recovery in all cases.

Can psychic trauma produce such a syndrome? The recent discussions of Schilder and Malamud¹⁴ offer support for such an hypothesis, but further work along such lines is necessary.

We must also raise the question of whether our low incidence of endocarditis may be due to the special clinic which kept the patient under close observation. It is possible that had the children been turned loose with no preventive cardiac supervision the incidence of endocarditis might have been higher. In a previous publication¹⁵ we have called attention to the excellent results and the few recurrences following from what we call the prophylactic treatment. By keeping the youngsters under constant observation, social and medical, and in-

interpreting the children's needs to the parents, obtaining cooperation from the school teacher avoiding the radio and thrilling movie, only six of the forty five patients developed a recurrence and three of these had not been faithful attendants at the clinic. Possibly this treatment may have of itself prevented endocarditis.

SUMMARY AND CONCLUSIONS

1 One hundred fifty cases of chorea have been registered in a special clinic during the last seven years.

2 Forty five of these who had also been hospitalized were selected at random for an intensive social service and medical study.

3 A clear cut history of rheumatic fever was obtained in only six cases. Fourteen additional cases gave a questionable rheumatic history.

4 Definite endocarditis developed in twelve patients. Five of these gave a history of true arthritis. In four a questionable history was obtained. In eleven of the twelve tonsils were present. In only one case of chorea without tonsils and without a history of a rheumatic infection did endocarditis develop.

5 The absence of endocarditis in the large group of choreic patients previously tonsillectomized and with no history of rheumatic fever strongly suggests that rheumatic fever and tonsillitis must play a far more important rôle in the etiology of endocarditis than does chorea.

6 A review of the histories of a control group of children with rheumatic endocarditis only rarely revealed a preceding history of uncomplicated chorea.

7 In our series chorea developed in mentally alert introverted children. These children are apparently predisposed by their particular constitution, heredity, environment and in some instances a possible endocrine imbalance. From our observations, there is little to favor a specific infectious origin of chorea. It seems to us that chorea is not a manifestation of rheumatic infection *per se* but that it is a clinical syndrome developing in a predisposed individual as a result of various psychic or physical insults. No matter what the exciting cause may be the choreic constitution seems of paramount importance. In our series chorea less frequently followed infection than it did psychic trauma resulting from exhausting psychic stimulation.

8 Our studies suggest

a. Chorea may be caused by rheumatic fever, but this is only one of many immediate causes. Psychic trauma seems far more important.

b. More important, too, are predisposing causes such as age, environment, temperament, special constitution, and possible endocrine factors.

c. Chorea should not be taken as an indication of rheumatic infection without other rheumatic manifestations.

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THE OCCURRENCE OF BLOOD FILLED CYSTS ON THE CARDIAC VALVES IN INFANCY

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ROUTINE postmortem examinations of the hearts of newborn infants and children in the pathologic laboratory at the University of Minnesota during a period of six months disclosed the rather frequent occurrence of small, blood filled elevations on the annular surfaces of the atrioventricular valves. In view of the fact that such findings may be misinterpreted for endocardial vegetations by one unacquainted with their anatomic significance, it seems advisable to discuss their frequency and benignity.

The presence of these cysts has received but slight attention by various investigators since Luschka described his first case in 1857. Two reports have appeared from this country. Apparently the condition has generally been recognized by those making neonatal pathologic examinations and has been considered an unimportant anatomic finding.

The present series of cases is based on postmortem examinations of seventy-two infants most of whom had been premature stillborn, or had died within the first week of life. A few older children were included. Of the seventy-two hearts twenty-three, or 32 per cent disclosed the presence of blood filled cysts on the cardiac valves. This figure corresponds well with the incidence of 25 per cent which Luschka reported in the first description of the condition, but it fails to agree with the higher figures of 60 to 80 per cent given by other investigators.

The age factor is important. The majority of subjects it will be noted, were full term infants who had either been stillborn or had died within the first week of life. The oldest child of the group with cysts on the cardiac valves was eight months of age the youngest a premature infant in the seventh month of gestation. Although the largest number of cysts (fourteen) occurring in any of these cases was found in the case of this premature infant none were found in a group of five hearts from fetuses six months old or less when the cardiac valves were studied microscopically in serial section. The causes of death in the entire series were principally trauma at birth congenital malformations, or among older children infection.

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Work done under the direction of Dr. E. T. Bell, Department of Pathology, University of Minnesota, Minneapolis, Minn. Submitted for publication, Aug. 10, 1934.

The site of predilection for these nodules is the atrioventricular valves, with the tricuspid valves slightly the favorite. In ten cases the tricuspid valves were affected, in six, both tricuspid and mitral valves, in five, the mitral alone, and in one case each, the aortic and pulmonic valves, respectively. The presence of a blood-filled cyst also was noted on a papillary muscle in one case. These cysts usually are found from 1 to 3 mm removed from the free edge of the valve on its auricular surface although they may occur anywhere on the surface of the leaflets. Cysts have been reported as having been present on the ventricular aspect of the atrioventricular valves, but they are infrequent. Occurrence at the line of closure has also been noted, although not in any of the present cases.



Fig 1—Heart of fetus in seventh month of gestation. Several blood-filled cysts are present on the auricular surface of the tricuspid valve.

It is usual for these cysts to be multiple, and, occasionally, they may be so closely grouped that the surface of the valve resembles a raspberry, which condition occurred in a case reported by Haushalter and Thury in which there were forty cysts on a single leaflet. In the present series eleven cysts were found on the tricuspid valves in one case and, in this same case also, three on the mitral valves. Cysts on the semilunar valves project on the ventricular aspect of the valve near the base of the cusp. There were but two such cases in the series.

The cysts varied in size from that of a pinpoint to 2 mm in diameter. The largest cyst reported was that by von Kahliden which measured 3 by 9 mm. They may be multilocular, and this is particularly apparent when they are seen microscopically. Grossly, they appear as dark, sharply circumscribed, rounded elevations on the smooth surface of the valve. They are easily visible in a good light with the naked

evo because of the contrast of the dark contents of the cyst against the pale background of the surface of the valve (Fig 1)

Before going into the histologic nature of these small elevations on the valves it might be well to review briefly the formation and normal structure of the cardiac valves. The atrioventricular valves of a new born infant are small projections from the cardiac wall which are composed of fibrous tissue and are covered by endothelium. This fibrous tissue is condensed to form a sort of plate, extending from the base of the valve at its attachment to the wall of the heart and thinning out toward the free edge of the leaflet, where only embryonic cellular tissue is found. This embryonic connective tissue is the material that forms the small nonpigmented elevations, known as Albin's nodules, on the surface of the cardiac valves of newborn infants. Some investigators claim that in late fetal life blood vessels may be demonstrated entering the

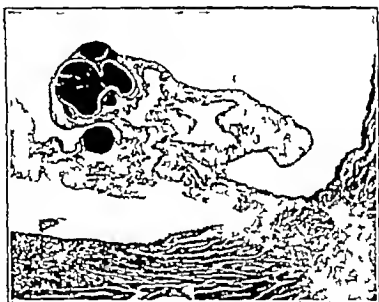


Fig 2—Section of the tricuspid valve of a fetus in the seventh month of gestation. The cysts are beneath the auricular endothelium and are filled with blood (X 5)

cardiac valves at their points of attachment to the wall of the heart. These may possibly be remnants of the vessels that nourished the muscle fibers which are normally found in the atrioventricular valves of fetuses but which are replaced in later embryonic life by fibrous tissue. Elastic fibers are more common in the semilunar valves, but they are found in the atrioventricular valves at their points of attachment and near the auricular surface. As the child grows older an increase of elastic tissue fibers is noted in the valves. The ventricular surface of the tricuspid and mitral valves is very uneven, owing to the insertion of the chordae tendinae between which are many furrows and small endothelial lined canals that penetrate into the substance of the valve toward the auricular surface in a more or less tortuous course.

These elevations on the atrioventricular valves were studied microscopically in four cases, and serial sections were made in three. The cyst

usually is a round, smooth-walled cavity, pushing up the endothelium of the surface of the valve beneath which it lies (Fig 2) The wall is composed of a few concentric layers of fibrous connective tissue, and the lining of the cyst is made up of a single layer of spindle-shaped cells with long, oval nuclei that cannot be distinguished from endothelium No muscle or elastic fibers can be seen in the capsule of the cyst The cysts may be multilocular or a series of communicating cavities If the pressure within them becomes too great, the partitions may rupture, thereby converting a group of cysts into one large cavity The endothelial lining may slough off into the contents of the cyst

It is not uncommon to see small out-pouchings from the periphery of the wall of the cyst, generally on the ventricular side In addition, several small, oval or elongated spaces are seen, which apparently are lined with endothelium, lying within the substance of the valve and running in a direction at right angles to the long axis of the leaflet

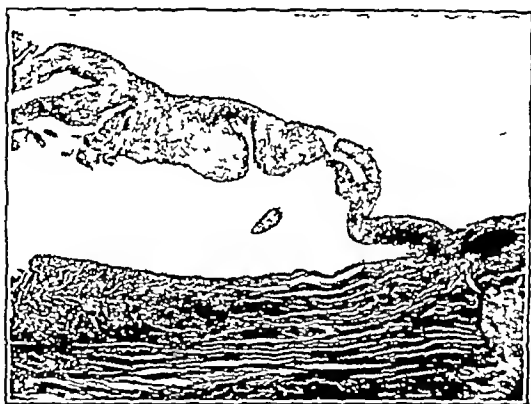


Fig 3—Endothelial-lined canals in the substance of the tricuspid valve, which open into the ventricular surface of the valve (X25)

(Fig 3) There are also many infoldings from the ventricular surface of the valve, lined by endothelium and directed toward the auricular surface These may be very tortuous in their course and never can be traced as far as the auricular surface They did not join cysts in any of the cases in this series

The contents of the cysts are chiefly erythrocytes, with occasional leucocytes and cells desquamated from the inner wall of the cavity According to Wegelin, this material becomes hyalinized as regression of the cysts occurs in later infancy, until, finally, all that remains to mark the former site of a blood-filled cyst is a little yellow pigment which is composed of iron from the erythrocytes in the substance of the valve In the process of involution, the wall of the cyst collapses, most of the blood is absorbed, and the walls of the endothelial-lined canals, originating from the ventricular surface of the valve, approximate until they merge with the valve substance

Four explanations have been offered for the origin of these cysts

1 They were considered to be hematomas, first by Elsasser, in 1845 and later by Luschka who thought them to be extravasations of blood into the noduli Albini of the valves. Trauma was supposed to play an important part in the production of these extravasations beneath the surfaces of the valves

2 Berti who first demonstrated the endothelial lining of these cysts, held that they are remnants of fetal valve vessels which had undergone cystic dilatation. Fahr and other investigators upheld this view, which received support from the fact that the greatest incidence of the cysts occurred on the atrioventricular valves since they were shown to be more vascular in fetal life than the semilunar valves. Also, the greatest incidence of the cysts corresponded in time with the period during which blood vessels were most prominent in the valves, the period of late fetal life

3 Nichols who published the first report of this condition in this country in 1908, said that they are angiomas. He found a somewhat similar condition in the bladder of the same patient, a child eighteen days old and he compared these findings to the more common angiomas in the skin of newborn infants.

4 Haushalter and Thurs advanced the theory that they are cystic dilatations on the ends of endothelial lined canals, whose origin is between the insertions of the chordae tendinae on the ventricular surface of the atrioventricular valves or, in the case of the semilunar valves, prolongations into the leaflets from the sinuses of Valsalva. This has since been substantiated by several more recent investigations. Ventricular systole forces blood into the canals and distends their terminations beneath the auricular endothelium forming blood filled cysts. Conditions favoring circulatory disturbance such as asphyxia or cerebral hemorrhage, were thought to account for the more frequent incidence of cysts in these cases.

At present, the final theory seems to be the most suitable for the explanation of the appearance of these blood filled cysts on cardiac valves. According to the proponents of this theory, the endothelial lined canals run a tortuous course from the ventricular surface of the valve toward the auricular surface in the case of the tricuspid and mitral valves. No connection of the cysts with vessels entering the valve at its base could be demonstrated by later workers as Berti and others had previously claimed and no connection with the general circulation was evidenced. There is no communication between the adjacent canals. The walls of these canals may be compressed so that all that is seen is a double layer of darkly staining endothelial cells. Compression of the canal is especially frequent as it enters the cyst usually on the ventricular side. Sections in the present series did not reveal any

canal that could be traced from its origin on the ventricular aspect of the valve to a union with the cyst although several sections showed canals adjacent to the cyst that suggested the possibility of such a condition. Because of the tortuosity of the canals, it was impossible to demonstrate the connection of canal and cyst in any case. Jonsson made models of these cysts, by the Born method of wax-plate reconstruction, and he was able to demonstrate that the cysts have numerous stalklike projections which extend from the cyst and open on the ventricular surface of the atrioventricular valves.

Cysts on the semilunar valves are formed from canals which take origin in the sinuses of Valsalva, near the attachment of the valve cusps. These cysts are present on the ventricular aspect of the cusps. Since the semilunar valves contain more elastic tissue than the atrioventricular valves, the structure of the semilunar valves is firmer and does not favor the formation of cysts within its more compact substance. As the child grows older, more elastic fibers appearing in these valves offer more resistance to the entrance of blood into the endothelial canals.

With the majority of infants these cysts disappear by the third month of extrauterine life, however, Wegelin has found them present in the cardiac valves of several adult patients.

No cardiac murmurs have been reported as a result of the presence of these blood-filled cysts on valve surfaces, and there is no evidence that they favor the development of endocarditis or of valvular insufficiency in later life.

SUMMARY

Small, blood-filled cysts occur not infrequently on the leaflets of the cardiac valves in the neonatal period. The best explanation for their origin is that they are cystic dilatations at the ends of endothelial-lined canals in the substance of the valves.

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SODIUM THIOCYANATE IN PROPHYLAXIS AND TREATMENT OF BACILLARY DYSENTERY WITH SPECIAL EMPHASIS UPON THE SHIGA TYPE

A PROGRESS REPORT COVERING THE FIRST TWO-YEAR PERIOD
OF A CLINICAL STUDY

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BECAUSE of the prevalence of bacillary dysentery of the Shiga and other types and the associated unfavorable mortality for a number of years physicians in the southern section of the United States have been seeking some specific treatment effective both in prophylaxis and therapeutics.

In June, 1932 one of us was privileged to observe at first hand the experimental work being done by Prof. A. C. Ivy, of the department of physiology Northwestern University. I will quote from his article more recently published "During the course of a study by Reid Anderson Stubblefield and Ivy¹ on the effect of filtrates of the Shiga bacillus on the motility of the gastrointestinal tract of dogs and during the course of a study by Crandall and Anderson on the use of sodium thiocyanate to determine free water in the body it was discovered that dogs which had received the thiocyanate four to five weeks previously failed to react in the usual manner after receiving lethal doses of the toxic filtrate. It was decided to investigate this accidental observation."

As a result of this observation Professor Ivy and his coworkers conducted an experiment involving some five hundred dogs and a series of rabbits with the following conclusions which formed the basis for our experiments on the human. The intravenous (20 mg. per kilogram) or oral (60 mg. per kilogram) administration of sodium thiocyanate from fourteen days to several (four or five) weeks prior to the administration of a Shiga dysentery toxic filtrate affords protection against the lethal action of the toxic filtrate in some but not all dogs and sodium thiocyanate (rhodanate) in this dosage is not dangerous for either intravenous use or by mouth.

Ivy suggested that from his experiments he believed sodium thiocyanate might not only prove to be effective in preventing Shiga dysentery in the human but would even possess therapeutic value as well if administered early enough after infection. After the onset of the disease and particularly in the stage of collapse or after ex-

¹From the Department of Physiology, University of Tennessee.

tensive, bloody diarrhea, Ivy considered that the drug would probably be relatively impotent and should be used only in connection with such supportive measures as parenteral administration of sodium chloride and glucose solutions and blood transfusions

The prophylactic dose of sodium thiocyanate recommended for trial by Ivy was 20 mg per kilogram ($1/3$ gram for each 22 pounds) of body weight, daily, administered in broken doses for three days. His experience indicated that this prophylactic treatment should afford protection for at least one month against an otherwise lethal dose of dysentery toxin. His data did not cover a longer period or the possibility that repeated infection might diminish or overcome the protection conferred by a single prophylactic course. After the onset of the disease, a single intravenous injection of 10 or 20 mg per kilogram of body weight of a 15 or 20 per cent solution of pure sodium thiocyanate was recommended.

Before beginning our experiments upon the human, we reviewed as fully as possible the essential pharmacology of the drug and the dosage. Sodium thiocyanate (rhodanate) has been used for a great number of conditions in the past. It has been advocated in the treatment of hypertension by many observers. Numerous reports, both favorable and unfavorable, have appeared in the last few years regarding its use in various psychiatric conditions. Numerous claims of toxicity also have appeared, but the drug in these cases was given in rather large doses and over a long period of time.

Goldring and Chassin² have reported toxic manifestations in thirteen patients with essential hypertension. The duration of the medication was from 7 to 69 days. The average daily dosage was 0.17 to 1.62 grams. The total dosage at the time of thiocyanate intoxication varied from 5.87 to 32.54 grams.

Egloff and his coworkers³ reported unfavorable results with thiocyanates in the treatment of hypertension, all of the patients showed some toxic manifestation usually at the end of from two to five days. Nausea was the most prominent symptom. Ten of the twenty-five patients complained of abdominal discomfort and diarrhea. One-gram daily doses were given for one week with smaller doses for two weeks longer. However, Black and his coworkers⁴ used as high as 45 grams daily over a long period of time on psychiatric patients with no toxic effects.

Paul,⁵ in a limited number of cases, found that sodium thiocyanate affected nemioses and arteriosclerosis. His tests were suggested because thiocyanate influences the aggregation of colloids in much the same way as the iodide ion, having a somewhat more solvent action. It also hastens the elimination of metals perhaps by rendering metallic protein compounds more soluble. It resembles the iodides also in producing coriza, acne, and other symptoms of iodism.

On the basis of the work of Lelloy⁶ who showed that the salt renders soluble the insoluble salts of calcium and magnesium thiocyanates have been used in the treatment of urinary calculi. Thiocyanate has also been used in chronic nephritis, migraine, as an antispasmodic for coughs and in recent years has been recommended in the painful crises of sickle cell anemia.

Following Ivy's recommendations we have in no instance given more than 20 mg. per kilogram intravenously or more than 60 mg. per kilogram orally in our study nor have we exceeded in any instance 1 gram per dose intravenously. In none of our cases have we had any toxic manifestations.

In order to assure us of the pure salt the Abbott Chemical Company under the direction of Professor Ivy prepared for us ampules of a 2 per cent solution. The first consignment contained 0.5 grains per ampule, later consignments contained 1 gram per ampule. We had no difficulty in obtaining the salt sufficiently pure for use by mouth.

In order to understand the purpose and scope of our clinical observations we feel that it is necessary to review briefly the etiology and symptomatology of bacillary dysentery as seen in the southern states.

According to Duval the term 'bacillary dysentery' implies the infection of the bowel with the specific bacillus which was discovered in 1895 by Shiga, who isolated and proved its causal relationship to the disease by positive agglutination reactions with the blood of the patients. Duval states and it has been our clinical experience that bacillary dysentery is not caused solely by the bacillus originally isolated by Shiga but by a number of bacilli which, though racially different belong to one and the same bacterial species. While all members of the group are pathogenic and cause what is known clinically as bacillary dysentery, the Shiga strain is regarded as the exciting cause of the more severe clinical form of the infection. On the other hand the sporadic type of the disease is commonly caused by some of the other bacilli of the group.

Bacillary dysentery may manifest itself as an acute subacute or chronic infection of the lower bowel characterized by fever, leucocytosis and diarrhea. It affects all ages but particularly the very old and the very young. It is most often seen as we approach the tropics.

Duval concludes that bacillary dysentery is of greatest severity in cities where it more commonly occurs. This has not been our experience. Our epidemics have been seen in the country districts where there is no sanitation where there is the cesspool type of toilet and uncremated houses where the water supply is bad dependence being placed mostly on cisterns and wells. Duval believes that the disease occurs coincident with or follows other infections of the intestine.

especially amebiasis, and that while in some patients the infection is slight, the digestive disturbance is severe. The intestinal and digestive conditions bear a general, but by no means a constant, relation to each other. While the bacilli usually disappear from the stools in two or three weeks after an attack, they may persist in the mucosa of the bowel for a much longer period. This fact explains relapses which occur months after the primary attack. Duval reports that the chronic cases give a history of exacerbations of the intestinal process which has remained without symptoms during the interval. He claims that if there are any reinfections they are exceedingly rare.

The excitant of bacillary dysentery is spread through the dejecta, included in the so-called water-borne diseases. It is distributed by food and flies. The true carrier may have bacilli in the intestines for months.

The pathology in bacillary dysentery is essentially an acute inflammatory process of the large intestine which is characterized by mucosal ulcerations and necrosis. It is most frequently limited to the large gut, but occasionally there is inflammation in the lower part of the small intestine. Pathologic lesions have been observed as far up as the pylorus. In the severe type early characteristic pathology is focal necrosis of the solitary follicles of the large bowel mucosa. Capillaries in the necrotic area become thrombosed, and the thrombi extend down to the exit of the vessels from the submucosa. Hemorrhages are due to the unplugging of the thrombosed capillaries in the floor of the ulcers. Perforation of the bowel is almost unknown in this disease. Bacillary dysentery does not give rise to septicemia.

The symptoms are usually a severe onset, sometimes convulsions, abdominal pains, listlessness, nausea, and vomiting. There are frequent stools at first, soon becoming bloody. There is usually a high, septic type of temperature.

The Shiga type is characterized even in the mild cases by from fifteen to twenty-five stools daily. The abdomen is usually tender and rigid. The effect of toxemia on the heart and pulse has been observed.

Symptoms of dehydration and fluid imbalance appear early. There is a leucocytosis which is usually quite high. The first signs of improvement are lowering of the leucocyte count and decreased number of stools. There is disappearance of blood from the stools and the appearance of fecal material. In some cases the disease becomes chronic with its succeeding symptom of inanition.

The diagnosis of dysentery is made from clinical symptoms of rapid onset and all symptoms above enumerated, particularly bloody and frequent stools. The type of dysentery is confirmed by stool examination.

The technic we employ in obtaining material for the stool examination is as follows. The patient is given an enema preferably of strong tea. After a short time a proctoscope is passed in the bowel and one of the ulcers found, with a sterile swab bloody material is taken from this ulcer. It has been demonstrated that these swabs may be taken in this manner put in a sterile test tube and kept as long as twelve or twenty four hours without impairing their ability to grow on culture media. This is mentioned because many of the cases occur away from laboratories where the material must be sent for examination.

The following technic is used for stool examination. The swab or a loopful of feces is placed in 10 cc of sterile saline. If feces is used, a loopful of this dilution is placed in a second tube of saline. Eosin methylene blue plates are streaked with this suspension. The next morning the plates are examined, and if any small, colorless colonies are seen, these are picked and transferred either to plain agar or EMB plate. This pure culture is then placed on the five sugars dextrose mannite maltose, saccharose and lactose. Identification of the organism is made from its reaction on the sugars. A hanging drop mount is also examined for motility. In doubtful cases agglutination tests are set up with immune serums.

TABLE I

B. DISSENTERIAL	DEXTROSE	MANNITE	MALTOSE	SACCHAROSE	LACTOSE
Shiga	plus	minus	minus	minus	minus
Flexner	plus	plus	plus	minus	minus
'Y' Hiss Parks	plus	plus	minus	minus	minus
Strong	plus	plus	minus	plus	minus

"Plus" equals acid—no gas. "Minus" equals no acid or gas.

Treatment generally recommended is. First and of greatest importance is the maintenance of fluid and mineral balance. This is best accomplished by injection of isotonic sodium chloride solution, and sometimes glucose solution, and by blood transfusion. All of these have been resorted to in our series of cases which are seen after the disease was well developed. None was used in the series of early cases reported in Osceola Ark. Opium is a very necessary and essential drug to give the patient some rest. Feeding is also as essential for this condition as it is for typhoid fever. All of our patients were fed with a sustaining protein diet, fairly low at first in carbohydrate which is gradually increased, and almost entirely lacking in fat which is increased as the patient improves.

The specific treatment used by us in years past and still recommended by some authors is polyvalent antidisenteric serums which if used at all should be given early. In our experience over a period of several years, such serums have proved of little if any value. There is a special serum for the Shiga type also on the market which we have used with little if any result. Bacteriophage has been used but

TABLE II
SEVERE CASES CLINICALLY DYSENTERY WITH NEGATIVE STOOL CULTURES, MEMPHIS, 1932-1933

NAME AGE SEX	HOSPITAL ADMISSION DATE	NUMBER AND CHARACTER OF STOOLS PRIOR TO ADMISSION	DURATION OF ILLNESS PRIOR TO ADMISSION	DIET—HOW GIVEN, AMOUNT GIVEN, DATES GIVEN	APPARENT EFFECT ON CHARACTER AND NUMBER OF STOOLS	APPARENT EFFECT ON TOXICITY AND COURSE OF ILLNESS, OTHER THERAPEUTIC MEASURES
L II 7 yr Female	B M H 7/25/33	10 to 60 daily, bloody with mucus	5 days	10 grains intravenously 7/25/33 and 7/26/33	None	Gradual decrease in 10 days
C C C 5 yr Male	M G H 8/2/33	15 to 20 daily, bloody	49 hr	7½ gr intravenously 6/26/33	None	Temperature came down gradually Parenteral fluids, tea enemata and paregoric
T M 4 yr Male	M G H 7/31/33	8 to 9 daily, bloody with mucus	5 days	5 gr intravenously 8/1/33 and 7½ gr 8/3/33	None	Seemed to respond to parenteral fluids and blood transfusion
B A 2 yr Female	M G H 7/8/33	?	?	34 gr intravenously 7/16/33	None	None
H O C 1 yr Male	M G H 6/24/33	10 to 12 daily, bloody with mucus	5 days	1 gr intravenously 6/24/33	None	None
C C 16 mo Female	M G H 6/10/33	5 to 6 daily, blood and mucus	36 hr	1½ gr intravenously 7/1 and 7/2/33	None	None
T D, Jr 17 mo Male	M G H 7/25/33	10 to 20 daily, blood and mucus	5 days	37½ gr intravenously 7/26/33	None	None
T J 7 yr Male	M G H 8/16/33	10 to 12 daily, blood and mucus	4 days	5 gr intravenously 8/17/33	Stools normal in 1 week	Child died 3 days after admission Questionable 7 days

TABLE II—CONT'D

NAME OF SEX	HOSPITAL ADMISSION DATE	NUMBER AND CHAR- ACTER OF STOOLS PRIOR TO ADMISSION	DURATION OF ILLNESS PRIOR TO ADMISSION	DOSE—HOW GIVEN AMOUNT GIVEN DATES GIVEN	APPARENT EFFECT ON CHARACTER AND VOLUME OF STOOLS	APPARENT EFFECT ON TOXICITY AND COURSE OF ILLNESS, OTHER THERAPEUTIC MEASURES
O. D. A. 1 yr Male	M G H 6/20/33	10 to 12 daily, blood and mucus	1 day	4 gr intravenously 7/11 and 7/12/33	None	None. Gradual improvement. Parenteral fluids; blood transfusion.
E. M. L. 2 yr Female	M G H 7/30/33	2 to 7 daily blood and mucus	8 hr	2 gr intravenously 4/4 and 8/4/33	None. Rapid improvement prior to giving drug	Temperature normal at end of 5 days. Drug however not given until fourth day. Parenteral fluids.
W. M., Jr. 1 yr Male	M G H 7/4/33	Many—bloody with mucus	5 days	1 gr intravenously 7/4 and 7/5/33	None. Gradual reduction	None. Temperature dropped and stools diminished 2 days after blood transfusion. Parenteral fluids.
C. L. J. yr Male	M G H 8/2/33	1 to 20 daily bloody with mucus	2 days	7½ gr intravenously 8/20/33	None	None. Gradual improvement. Blood transfusion.
M. B. yr Female	M G H 7/16/33	Frequent bloody stools with mucus	1 hr	37½ gr intravenously 7/16 and 7/20/33	None	High fever and convulsions on admission. Removed against advice 7/20/33. No improvement up to this time.
M. C. 13 mo. Female	M G H 8/1/33	10 to 12 daily bloody with mucus	9 days	2½ gr intravenously 8/20/33	None	None. Prolonged course complicated by much vomiting. Parenteral fluids.
L. R. 1 yr Female	M G H 7/11/33	Frequent bloody with mucus	9 hr	5 gr intravenously 7/11/33	None	None. Prolonged toxic course complicated by pyelitis. Urotropine. Parenteral fluids. Stimulants.

TABLE III
SEVERE CASES WITH POSITIVE SHIGA CULTURES, 1932-1933

NAME AGE SEX	HOSPITAL ADMISSION DATE	NUMBER AND CHAR- ACTER OF STOOLS PRIOR TO ADMISSION	DURATION OF ILLNESS PRIOR TO ADMISSION	NASON—HOW GIVEN, AMOUNT GIVEN, DATES GIVEN	APPARENT EFFECT ON CHARACTER AND NUM- BER OF STOOLS	APPARENT EFFECT ON TOXICITY AND COURSE OF ILLNESS, OTHER THERAPEUTIC MEASURES
I D 17 mo Male	B M H 8/12/32	20 a day with blood and mucus	4 days	7 gr intravenously 8/12 and 8/13/32	None	Patient did not respond at all to therapy and died 8/14/32
D M 9 mo Female	B M H 9/26/32	10 to 15 a day, bloody with mucus	6 days	11 gr intravenously 9/28, 5 cc 9/30/32	None	Patient died 10/5/32 Toxæ course complicated by bilateral otitis media
D E D 13 mo Male	B M H 9/16/32	10 to 15 daily, bloody with mucus	2 wk	3.5 gr intravenously 9/16 and 9/17/32	Gradual reduction daily for 1 week	At end of a week patient developed an upper respiratory infection, complicated by pyelitis with in- crease in number of stools with no blood Urotropine, sodium, and phosphate Child died 10/19/32
B II 3 yr Female	M G II 10/17/32	20 to 25 daily, bloody with mucus	3 days	7.5 gr intravenously 10/17/32	None	Did not seem very sick for 1 week, then very toxic Gradual recovery Parenteral fluids
L II 3 yr Male	M G II 10/11/32	10 to 15 daily, blood and mucus, pro- lapse of rectum	7 days	7.5 gr intravenously 10/14/32	None	None Death occurred 8/25/32 Par- enteral fluids Blood transfusions
M E D 1 yr Female	B M II 8/20/33	8 to 10 daily, bloody with mucus	3 wk	20 mg per kilogram body weight intra- venously 8/20, 8/23 and 8/24/33	None	Temperature normal in 24 hours after first dose of drug Dis- charged 9/18/33
D M 7 yr Male	B M II 9/9/33	15 to 20 daily, bloody with mucus	48 hr	12 gr intravenously 9/9, 9/10, and 9/11/33	Stools normal within 5 days	Died 24 hours after admission Par- enteral fluids
B E 1 yr Male	B M H 5/23/33	20 to 24 daily, bloody with mucus	3 days	20 mg per kilogram body weight intra- venously 5/23/33	None	

TABLE III—CONT'D

NAME AGE SEX	HOSPITAL ADMISSION DATE	NUMBER AND CHARACTER OF STOOLS PRIOR TO ADMISSION	DURATION OF ILLNESS PRIOR TO ADMISSION	DIAGNOSIS—HOW GIVEN AMOUNT GIVEN, DATE GIVEN	APPARENT EFFECT ON CHARACTER AND NUMBER OF STOOLS	APPARENT EFFECT ON TOXICITY AND COURSE OF ILLNESS OTHER THERAPEUTIC MEASURES
L. H. 12 yr Male	R. M. H. 5/28/33	5 daily with pus, blood and mucus	6 days	15 gr intravenously 5/28/33	No immediate, gradual reduction in number	Toxicity decreased in 3 days. Had a concomitant pyelitis. Parenteral fluids, blood transfusion urtione intravenously
M. D. 2½ yr Female	R. M. H. 7/1/33	12 to 15 daily watery no blood	48 hr	7½ gr intravenously 7/3 and 4 gr 7/4/33	None. Gradual reduction	Concomitant pyelitis. Gradual decrease in toxicity. Parenteral fluids. Prescription for pyelitis ten enemas.
P. Y. 2 yr Female	R. M. H. 6/20/33	20 daily with blood and mucus	7 days	6 gr intravenously 6/27 and 6/28/33	None. Gradual reduction	Gradual decrease in toxicity. Parenteral fluids. Blood transfusion.
M. E. S. 9 yr Female	M. G. H. 5/18/33	20 to 21 daily with blood and mucus	48 hr	15 gr intravenously on 5/24/33	None. Frequent bloody stools over 2 months	In hospital over 2 months. Returned 8/15/33 with stricture of rectum Parenteral fluids. Blood transfusion
V. F. 3 yr Female	M. G. H. 5/24/33	8 to 10 daily blood and mucus	7 days	5 gr intravenously 5/24/33	None	2 weeks of fluctuating fever then rapid return to normal
J. F. 6 yr Male	M. G. H. 5/24/33	12 to 1 daily with blood and mucus	6 days	7½ gr intravenously 5/26/33 and 5/27/33	Stools decreased markedly 2 days after drug was given	Gradual decrease in toxicity
O. S. 11 yr Male	M. G. H. 7/24/33	Severe diarrhea with blood and mucus	24 hr	15 gr intravenously 5/26 and 5/27/33	None. Many bloody stools daily	5/28/33 became emaciated and delirious and died in a few hours.
R. J. J. 10 mo Female	M. G. H. 6/2/33	Frequent bloody stools and mucus	4 days	7½ gr intravenously 6/4/33	None. 7 to 8 bloody stools daily for 2 weeks	Septic temperature for 2 weeks. Poor parental fluids. Two blood transfusions

TABLE IV
SEVERE CASES WITH POSITIVE FLYNNER STRONG CULTURES, MEMPHIS, 1932-1933

NAME AGE SEX	HOSPITAL ADMISSION DATE	NUMBER AND CHARACTER OF STOOLS PRIOR TO ADMISSION	DURATION OF ILLNESS PRIOR TO ADMISSION	NASCV—HOW GIVEN, AMOUNT GIVEN, DATES GIVEN	APPARENT EFFECT ON CHARACTER AND NUMBER OF STOOLS	PARENT EFFECT ON TOXICITY AND COURSE OF ILLNESS, OTHER THERAPEUTIC MEASURES
W G 18 mo Male	B M II 9/29/32	13 to 21 a day, with blood and mucus	8 days	7 gr intravenously, 9/29, 10/3, and 10/15	Rapid decrease	Gradual decrease in toxicity transfusion
L P 2 yr Female	B M II 8/8/32	?	?	4 gr intravenously 8/10/32	None	Patient died 8/12/32
P W 14 yr Female	B M II 9/10/32	12 to 14 a day, with blood and mucus	5 days	7 1/2 gr intravenously 9/30/32, 5 gr 10/5/32	None	Toxicity gradually lessened Discharged at the end of 2 weeks
M E W 17 mo Female	B M II 10/13/32	15 to 20 a day, bloody with mucus	2 mo	7 1/2 gr intravenously 10/13/32	None	Child died in less than 24 hours Bronchopneumonia
C C 2 yr Male	M G II 7/24/32	12 to 13 a day, bloody with mucus	3 days	5 gr intravenously 5/24/33	None	Child had several convulsions Temperature 106° F, carpopedal spasm Death within 29 hours Treatment for tetany
M W 2 yr Female	M G II 8/5/32	12 to 15 a day, bloody with mucus	9 days	7 1/2 gr intravenously 8/5/32	No immediate	Very toxic for 11 days Developed pyelitis Discharged 3 weeks after admission
O L K 3 yr Male	B M II 4/22/33	25 to 30 a day, bloody with mucus	10 days	7 1/2 gr intravenously 4/24 and 4/25/33	No immediate	Ran a rather toxic course Developed malaria following blood transfusion on 5/9/33 Quinine, atabrine, plasmochin, parenteral fluids
I W 15 mo Male	B M II 7/26/32	25 to 30 a day bloody with mucus	48 hr	4 gr intravenously 5/27/33	Immediate reduction in 24 hours	5/29/33 urine full of pus with no crudescence of diarrhea Subsided when pyelitis cleared up Paren- teral fluids, uritone intravenously
B M 2 yr Female	M G II 5/1/33	3 to 6 daily, with pus, blood, and mucus	5 days	7 1/2 gr intravenously 7/3, 7/7, 7/10/33	Stools never very numerous	Gradual decrease in toxicity Could not be attributed to drug

TABLE I

EPIDEMIC OF BACILLARY DYSENTERY IN OSCEOLA, ARK. SPRING AND SUMMER OF 1933 SUMMARY OF CASES

Clinical cases, 30 positive Shiga cultures, 24 severely toxic, 14 moderately toxic, 13 mild, 2, 1 (?), deaths, 6 mortality, 20 per cent
 Comment Five of the six patients who died did not receive the drug

CASES	DEGREE OF TOXICITY	DATE OF ONSET	DATE GIVEN DRUG	STOOLS DIMINISHED AFTER DRUG	TOXICITY DISAPPEARED	DATE DISMISSED	CULTURE	AGE IN YR.	SEX
1	Severe	5/11/33	None given	-	-	Died 5/21/33	None	1	M
2	Severe	5/23/33	None given	-	-	Died 5/20/33	Shiga	3	M
3	Severe	5/22/33	5/22/33	3 days	-	9/10/33	Shiga	13	M
4	Severe	5/22/33	5/22/33	- days	3 days	6/10/33	Shiga	7	M
	Severe	5/22/33	5/22/33	1 day	3 days	6/10/33	Shiga	8	F
6	Severe	6/1/33	6/1/33	4 days	-	6/14/33	Shiga	14	F
7	Severe	6/1/33	6/1/33	-	-	Died 6/11/33	Shiga	4	M
8	Severe	6/9/33	6/8/33	-	-	6/12/33	Shiga	8	F
9	Severe	6/9/33	6/9/33	4 hr	-	Died 6/12/33	Shiga	13	M
10	Severe	6/16/33	None given	-	-	Died 6/28/33	Shiga	13	F
11	Severe	6/20/33	6/18/33	24 hr	2 days	Died 6/22/33	Shiga	30	M
12	Severe	6/24/33	None given	-	-	Died 7/1/33	Shiga	2	M
13	Severe	6/24/33	6/24/33	3 days	2 days	Died 7/1/33	Shiga	4	M
14	Severe	6/28/33	None given	-	-	Died 6/14/33	Shiga	0	F
15	Mild	6/10/33	6/10/33	3 days	4 days	6/15/33	Shiga	25	M
16	Moderate	6/12/33	6/13/33	24 hr	24 hr	6/15/33	Shiga	0	F
17	Moderate	5/14/33	5/15/33	Same day	3 days	6/1/33	Shiga	2	F
19	Moderate	6/23/33	6/26/33	12 hr	1 day	7/1/33	Shiga	28	M
19	Moderate	6/25/33	6/26/33	12 hr	1 day	7/2/33	Shiga	9	F
20	Moderate	6/28/33	6/28/33	12 hr	1 day	7/2/33	Shiga	6	M
21	Moderate	6/28/33	6/28/33	12 hr	1 day	7/2/33	Shiga	13	F
22	Moderate	6/28/33	6/28/33	12 hr	1 day	7/2/33	Shiga	3	F
23	Moderate	7/1/33	7/1/33	12 hr	1 day	7/10/33	Shiga	4	F
23	Moderate	7/9/33	7/11/33	24 hr	1 day	7/16/33	Negative	7	M
24	Moderate	7/9/33	7/10/33	24 hr	1 day	7/16/33	Negative	20	M
25	Moderate	7/11/33	7/11/33	2 hr	12 hr	7/14/33	Negative	29	F
26	Moderate	7/7/33	7/16/33	12 hr	12 hr	7/14/33	Negative	4	F
27	Mild	7/7/33	7/10/33	2 hr	6 hr	7/14/33	Negative	25	F
28	Moderate	7/7/33	7/11/33	48 hr	7 days	7/24/33	Typoid	2	M
29	Moderate	7/13/33	7/13/33	6 hr	1 day	7/15/33	Shiga	7	M
30	?	6/10/33	6/10/33	?	?	?	Shiga	Adult	F

is discarded now by most men Both Duval⁷ and Silverman⁸ of New Orleans recommend the use of an autogenous vaccine given in large doses in all the chronic cases

After reviewing the above considerations, we decided upon the following routine which was instituted in June, 1932, in the Children's Department of the Memphis General Hospital and the Children's Department of the Baptist Memorial Hospital and by a few selected private physicians Every patient with bloody diarrhea entering the charity service of these institutions was to be given sodium thiocyanate, 20 mg per kilogram of body weight, intravenously, the daily dose not to exceed 1 gram If there was no improvement, the intravenous injections were to be repeated for three successive days, never longer

In addition, the recognized forms of treatment, such as, maintaining the fluid balance, blood transfusion, opium, and proper diet were to be maintained No other specific form of treatment was to be used All persons exposed by direct contact with the patient were to be fed the drug by mouth, 1/3 grain, 60 mg, per kilogram for three successive days In none of our cases has the total dose of thiocyanate exceeded 1 gram There have been no toxic reactions in our series not even the toxic rash which is sometimes seen The experiment has now extended over a period of two years Tables II, III, IV, V and VI give in detail the results, our conclusions follow

TABLE VI
MORTALITY OF CASES TREATED WITH SODIUM THIOCYANATE

	TOTAL CASES	DEATHS	MORTALITY
Massey's Series	25	1	4
Memphis Shiga	17	6	35.3%
Flexner Strong	9	3	33.3%
Proteus	2	0	0
Negative Cultures Clinically			
Dysentery	18	1	5.5%
Parenteral Diarrheas	2	0	0
Total	73	10	13.7%

SUMMARY

Seventy-three cases of bloody diarrhea are reported in which 20 mg per kilogram of body weight of a 2 per cent solution of pure sodium thiocyanate (rhodanate) was given intravenously Some of the patients were given but one dose, others as many as three successive doses depending upon the clinical manifestations following the first injection In addition all persons in direct contact with the patients were given 1/3 gr of the pure salt for each kilogram of body weight daily in broken doses of three successive days In several instances where there was a history of contact and the individual showed slight

early symptoms, such as diarrhea, pain in the abdomen, or vomiting the drug was used intravenously in the same dosage as recommended for treatment for the purpose of prophylaxis

The mortality for all patients given the drug was 13.7 per cent. Of the seventeen cases of Shiga dysentery which were treated in the Memphis hospitals during 1932 and 1933 with thiocyanate, the mortality was 35.3 per cent. None of these patients received the drug within the first twenty-four hours. In the epidemic which occurred in Osceola, Ark. in 1933, twenty-five patients were given the drug by Dr. L. D. Massey. Practically all of these patients received the drug within the first twenty-four hours, there was prompt decrease in the number of stools and the amount of blood present in them. Concomitant with this result was rapid decrease in toxicity. Of the patients treated in the Osceola epidemic only one who received the drug died. Five patients who did not receive the drug died. No definite benefit was seen from the administration of the drug to nine patients with Flexner Strong dysentery or to eighteen patients with clinical dysentery who had negative stool cultures. However, the drug was administered late in the disease in practically all of these latter cases.

CONCLUSIONS

1 Sodium thiocyanate (rhodanate) in the dosage of $1/3$ gr. per kilogram of body weight orally seems to have definite prophylactic value in Shiga dysentery.

2 If given intravenously in the dosage of 20 mg. per kilogram of body weight on successive days within twenty-four hours after onset in Shiga dysentery, sodium thiocyanate (rhodanate) seems to have marked beneficial effect.

3 Sodium thiocyanate (rhodanate) does not appear to influence dysentery due to other strains. However, these types of dysentery are usually mild in onset and in all of our work have been in progress several days before being seen.

4 Tables II and III indicate that the drug does not influence either the course of the disease or the mortality when it is given as late as thirty hours after onset. It is probably of little value when given after twenty-four hours. Table IV would seem to indicate that when the drug is given early, not later than twenty-four hours after onset it has a decided value in influencing both the mortality and the severe toxic course of Shiga dysentery.

5 Our mortality experience with the new treatment in the charity services of the Memphis General Hospital and Baptist Memorial Hospital has not shown a material improvement over previous years. This is attributable in our judgment, to the fact that the cases in such services are rarely seen until the disease has been in progress for

more than twenty-four hours. It is noteworthy that in the Osceola epidemic (private cases) where the drug was administered at the first appearance of diarrhea, only one patient in twenty-six died. The effectiveness of sodium thiocyanate therapy clearly depends upon its early use.

6. No claim for sodium thiocyanate (rhodanate) as a specific, either in the prevention or in the treatment of bacillary dysentery, is made by the authors as a result of this brief clinical experience. Our preliminary results, however, lead us to believe that our method of treatment is worth further trial, and we hope to publish at a later date a much more complete clinical report in which a larger number of institutions and physicians have participated.

We wish to extend our thanks to Dr. L. D. Massey, Osceola, Ark., and Miss Helon Peck, chief of the clinical laboratory division, Baptist Memorial Hospital, for their assistance in this clinical presentation.

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THE PULMONARY LESIONS ASSOCIATED WITH INTRAUTERINE ASPHYXIA

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ASPHYXIA is the most frequent and the most important of all pathologic processes. This is true because respiration—the exchange of oxygen and carbon dioxide and the production of energy—is the most fundamental process of life. (Yandell Henderson¹) In utero the fetal blood contained in the placenta is constantly undergoing the changes that in the adult occur in the lungs. Any interference with the placental circulation results in varying degrees of intrauterine asphyxia characterized anatomically by petechial to fairly large hemorrhages in most of the organs of the body and serosanguineous transudates in the serous cavities.

In recent years certain of the pulmonary lesions associated with intrauterine asphyxia have received much consideration. In 1931 Farber and Sweet reviewed the controversial literature concerning intrauterine asphyxia as a cause of premature respiratory movements in utero and stressed the fact that the presence of amniotic sac contents in large quantities in the lungs of asphyxiated infants indicates the occurrence of such premature attempts at respiration. That the aspiration of amniotic fluid, especially if it is infected, may have an added significance as a cause of antenatal pneumonia has been emphasized by Thavsen,² Browne,⁴ Johnson and Meyer³ and Warwick.⁶ It would seem therefore that a more general consideration of the various pulmonary lesions that are found in infants who present either clinical or anatomic evidences of asphyxia might be valuable. The following study describes the various pulmonary lesions found in asphyxiated stillborn and newborn infants and endeavors to show the relationship between these lesions and the conditions of asphyxia.

MATERIAL AND METHOD OF STUDY

The study is based on 100 consecutive autopsies performed upon infants stillborn or dying during the first two weeks of life. In this series thirty-eight were stillborn, thirteen of whom were premature, sixty-two were newborn, twelve of whom were premature. The great majority of these necropsies were performed by the writer. They were

From the Hoagland Laboratory, Department of Pathology, the Long Island College of Medicine.

conducted with as much care and thoroughness as is customary in the examination of adult bodies in an effort to reduce the number of unexplained deaths to a small figure. The Benecke technic⁷ was used in opening the skull, thus avoiding any unnecessary postmortem destruction of the falx cerebri and tentorium. The base of the skull was examined for fractures, while the spine was examined both for fractures and separation of the vertebrae. After careful examination in situ of the thoracic, abdominal, and pelvic organs, these were removed in toto. They were then studied from their posterior aspect so that lesions of the adrenals, kidneys, or ureters could be seen in their normal anatomic relationships. The individual organs were then examined in the usual manner. Microscopic studies were made of all of the tissues including the brain and cord, but especial attention was paid to the lung sections on which hematoxylin and eosin, Gram, Giemsa, and sudan III methods of staining were used.

The clinical data were obtained through the courtesy of Prof. Carl H. Laws, of the Department of Pediatrics, Long Island College of Medicine.

CAUSES OF NEONATAL DEATH

It is generally accepted that the postmortem findings of intrauterine asphyxia, aside from the characteristic petechial serosal hemorrhages, are those of an intense venous congestion. The right heart is engorged, and the large thoracic vessels, sinuses of the dura, and hepatic vessels are markedly distended. Edema of the brain and brain stem is also a very common finding in asphyxiated infants. The above anatomic findings, if not explained by some other cause, can usually be supported by the clinical evidence of asphyxia.

In Table I the apparent causes of death as determined by autopsy are listed. In thirty-five cases the usual anatomic lesions of asphyxia were found alone, and therefore asphyxia was considered the cause.

TABLE I

APPARENT CAUSE OF DEATH	CASES	CASES SHOWING ANATOMIC LESIONS OF INTRAUTERINE ASPHYXIA
Intrauterine asphyxia (alone)	35	35
Prematurity	25	12
*Intracranial hemorrhages with tentorial tear	9	9
Incomplete tentorial tear (no hemorrhage)	6	6
*Adrenal hemorrhage	6	6
Congenital anomalies	8	4
Infections	4	2
Congenital pneumonia	6	5
Hemorrhagic disease of newborn	1	1
Total	100	80

*It is perhaps significant that all of the cases of intracranial and adrenal hemorrhages showed lesions of asphyxia in other organs.

of death, of the remaining sixty five cases showing birth injuries or other conditions, forty five also revealed anatomic lesions of asphyxia.

CAUSES OF INTRAUTERINE ASPHYXIA

Certain abnormal clinical conditions are commonly considered as causes of asphyxia. Their occurrence in the eighty cases that showed anatomic evidence of asphyxia is indicated in Table II.

TABLE II

Breech delivery	20
Coll around neck	10
Prolapsed cord	8
Premature separation of placenta	8
Placenta previa	7
Maternal toxemia	1
Prolonged dry labor	5
Narcosis of infant	2
Unknown	17
Total	80

Instrumental operative interference is not listed as a cause of this pathologic process because when such a procedure was employed the case already presented one of the above conditions which in itself may have been the cause of asphyxia.

THE PULMONARY LESIONS

This series of 100 unselected cases revealed on microscopic examination changes in the lungs that can be described under the following three headings: (1) aspirated amniotic sac contents, (2) desquamative encephalitis, (3) congenital pneumonia.

Atelectasis was not included among the important histologic observations because in this series it was not a prominent histologic feature. The term "atelectasis" which refers to the state of expansion of the lungs is a relatively loose term and may include any condition from partial dilatation to complete nonexpansion of the alveoli. Little information concerning the degree of expansion can be ascertained by gross examination of the lungs. In this series of 100 cases extensive and complete atelectasis was not found in a single instance in the lungs of the new born or stillborn infants. Even in the case of stillborn infants, while occasional foci showed complete lack of expansion, most of the alveoli were more or less distended by blood, serum, amniotic sac contents, or desquamated pulmonary epithelium. Not infrequently the hemorrhages were confined to small wedge shaped areas which resembled infarcts.

From these findings one must conclude that most or probably all alveoli are potentially capable of expansion whether the agent be air, fluid, blood, or some cellular constituents. Hence in this series of cases atelectasis was not considered an important factor in asphyxia or

neonatal death, but merely as indicative that the air spaces had not been properly ventilated. A distinction, however, should be made between atelectasis and undeveloped pulmonary tissue seen frequently in premature infants and occasionally in full-term infants.

1 *Aspirated Amniotic Sac Contents*—Amniotic sac contents were found in 50 per cent of all cases. In 39 per cent they were found in very small quantities. In 11 per cent they were found in large quantities filling the alveolar spaces, ducts, and bronchioles, and in all of these cases there was marked clinical evidence of asphyxia. The most reliable and constant evidence of aspirated amniotic fluid is the presence of cornified desquamated epithelial cells from the skin of the fetus. In

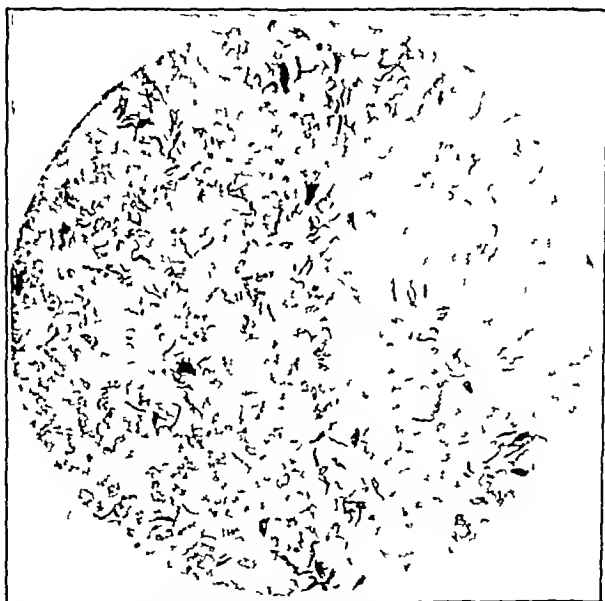


Fig 1—Aspiration of amniotic sac contents. The section of lung shows large numbers of cornified epithelial cells in the alveoli.

hematoxylin and eosin sections they may appear as purple staining irregularly shaped, wavy structures having a wider central portion with pointed ends, if seen from their narrow aspect. On their flat surface they appear as gray- to violet staining structures having a broad central portion. No nuclei are discernible. Lanugo hairs from the fetus, vernix caseosa, and bile salts are also present at times.

When large quantities of amniotic fluid were found in the lungs, the amount of mucus in the trachea and bronchi was notably less than in the other groups of this series, an observation the significance of which will be discussed below. The following case illustrates the aspiration of large quantities of amniotic sac contents.

Baby R., a stillborn infant, weighing 3,400 gm was delivered spontaneously as an LOA after 16½ hours of labor. The fetal heart was not heard for several hours before delivery. There was a loop of cord twisted around the right knee and leg. At autopsy the mouth larynx trachea and bronchi contained a small amount of yellowish brown, gelatinous, mucoid material. Microscopic sections of the lungs revealed large quantities of desquamated cornified epidermal cells (Fig 1)

2 *Desquamative Anaeriosis*—The term “desquamative anaeriosis” is proposed as being descriptive of that form of pulmonary lesion noted in asphyxia in which large quantities of desquamated epithelial cells are found, not only occluding the bronchioles and ducts, but completely filling and distending many alveolar spaces. DeLee,⁸ in a general discussion of asphyxia neonatorum, suggested that the term “anaeriosis”



Fig 1.—Desquamative anaeriosis. Desquamated bronchiole epithelial cells filling a bronchiole and adjacent alveolar spaces.

be substituted for ‘asphyxiation’ which is etymologically incorrect because it means without pulse. The term ‘anaeriosis’ from *an*, privative + *aer* air + *osis* condition of, expresses the state of the infant. The qualifying term ‘desquamative’ which I have added, describes the pathologic process which, as will appear later may be both a result and a cause of asphyxia.

In these cases there is an intense congestion and edema of the submucosa which results in cloudy swelling and fatty degeneration and even detachment of the bronchial epithelial cells. During respiration the detached mucosa may fold upon itself, or a complete telescoping of the mucous membrane may result thus obstructing the bronchi or bronchi

oles In microscopic sections the lumina of some of the bronchioles were occasionally found to be plugged by a complete ring of bronchial epithelium which undoubtedly had become separated from its submucosa. A much more frequent and serious consequence of epithelial desquamation consists of the filling of the smaller air passages and particularly the alveolar spaces with these desquamated cells.

A pink-staining membrane was frequently found lining the small bronchioles and alveolar ducts in cases of this group. This appearance was attributed to degenerative changes in the lining epithelium and the accumulation of cellular debris containing fat droplets, a feature which will be discussed below.

This group of cases showing desquamative anaeriosis, of which eighteen were newborn, comprised 31 per cent of the entire series. As the term implies, these cases were always associated with a marked degree of intrauterine asphyxia. The following case illustrates this pathologic condition.

Baby E, a stillborn infant, weighing 2,360 gm., was delivered spontaneously after the mother, a multipara, had had three eclamptic convulsions. She was admitted by ambulance, and no history of the first and second stages of labor could be ascertained. The third stage lasted one half hour. At autopsy a few cubic centimeters of blood tinged fluid were found in the peritoneal cavity and pericardial sac. Numerous petechial hemorrhages were found on the epicardial surface of the heart. Many small pial and subarachnoid hemorrhages were found. There were superficial tears of the tentorium on both sides, but no gross hemorrhage was noted. The brain and cord showed edema. The gross appearance of the lungs was not unusual for a stillborn infant except that the mucous membranes of the trachea and bronchi were deeply congested. Microscopic sections of the lungs showed large quantities of desquamated bronchial epithelial cells in the smaller air passages and completely filling and distending many alveolar spaces (Fig. 2).

3 *Congenital Pneumonia*—This group includes those cases of stillborn or newborn infants dying during the first two weeks of life, who showed an acute inflammatory exudate in the lungs. No instance of 'pneumonia alba' of congenital syphilis was encountered. In the series of 100 cases reported here, only 6 per cent showed definite pneumonia, and of these only one case occurred in a stillborn infant. In the lung sections from infants in whom there was no pneumonia, bacteria were rarely found (4.1 per cent), whereas in 83 per cent of the pneumonia cases bacteria were demonstrated. Of this latter group the only case of pneumonia in which no bacteria were found was in the stillborn infant. The organisms consisted of gram positive bacilli and cocci frequently arranged in clumps and often enmeshed in the debris of the smaller bronchioles and alveolar ducts. In two of the cases bacteria were also found diffusely scattered throughout the alveolar spaces. No bacteria were found in the lumina of the blood vessels. Amniotic sac contents were found associated with pneumonia only occasionally.

and then in very small amounts. Only one case, a stillborn infant, showed a considerable collection of this material. The following case is typical of this group.

Baby T., a premature infant of 7½ months gestation, was delivered spontaneously following one hour and fifteen minutes of labor. The mother, a para v, had diabetes and nephritis. Resuscitation of the infant was spontaneous, and it had a strong cry. The infant vomited repeatedly after birth. On the third day he developed severe cyanotic attacks and expired. At autopsy numerous small subpleural hemorrhages were found in both lungs. On section the lungs were found to be atelectatic in appearance and fleshlike in consistence. No gross evidence of pneumonia could be seen. The adrenals were hemorrhagic and the remaining organs showed marked congestion. Microscopic section of the lungs revealed a purulent

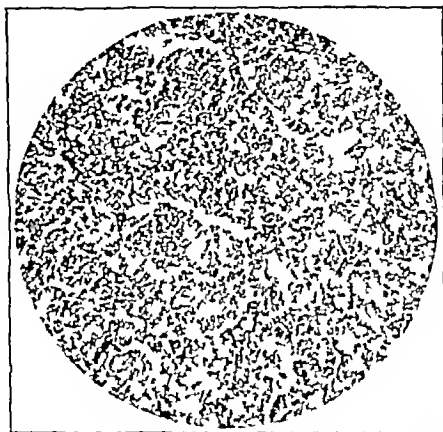


Fig. 3—Congenital pneumonia. An acute purulent exudate in the bronchioles and alveoli.

exudate in the bronchi and alveolar spaces in which bacteria were found. No amniotic sac contents were noted. The microscopic lesions were patchy in distribution (Fig. 3).

DISCUSSION

Of the sixty-two cases of newborn infants dying within the first two weeks of life, fifty showed clinical evidence of asphyxia. Of the latter, twenty-three cases or 46 per cent, showed pulmonary lesions, such as aspirated amniotic sac contents and desquamative anserosis to which postnatal asphyxia might be attributed. In five of these cases large quantities of amniotic sac contents were found in the lungs, and eighteen showed the findings of desquamative anserosis. As has been shown above both of these pathologic conditions are brought about by intra

uterine asphyxia, and their persistence in extrauterine life may be the cause of respiratory embarrassment. These processes, therefore, may be both the effect and cause of asphyxia.

Faerber and Sweet² have given an excellent discussion of the means of recognition and the significance of the occurrence of amniotic sac contents in 88 per cent of their series of 124 infants who had lived from two hours to five weeks. Large quantities of this material were found in 15 per cent of their series. Warwick³ in 240 consecutive autopsies upon infants, stillborn or dying during the first two weeks of life, found one or more of the constituents of amniotic fluid in 73 per cent of her series.

It is noteworthy that of the cases in my series only eleven, of which five were newborn, showed large quantities of aspirated amniotic fluid in spite of the fact that a great majority of the cases presented evidence of intrauterine asphyxia. When one considers that the mucus in the upper air passages in newborn infants varies in quantity and may be very abundant, it seems possible that, by occluding the larger air passages, it may act as nature's barrier against aspiration of the amniotic fluid. The fact that no such barrier was present in the cases of this group lends support to this theory.

In these eleven cases a small to moderate quantity of desquamated bronchial epithelial cells were also found in the alveolar spaces, but cases in which large quantities of these cells filled the alveolar spaces (desquamative anaeriosis) showed little or no evidence of amniotic sac contents.

In my series the findings designated as desquamative anaeriosis and interpreted as histologic evidence of asphyxia were always associated with clinical evidence of intrauterine asphyxia. This anatomic diagnosis was made only when large quantities of desquamated bronchial epithelial cells were found in many of the alveolar spaces. This lesion, as previously mentioned, may be an important cause of extrauterine respiratory embarrassment and has therefore an important bearing on the problems of resuscitation. The mechanical respirators, or instruments of the Flagg type⁴ designed for the clearing of the upper air passages and insufflation of oxygen and carbon dioxide, may prove inadequate in such cases.

Hyaline membranes such as were noted in the group of cases showing desquamative anaeriosis have been studied by several investigators. Johnson and Meyer observed these membranes lining alveolar ducts and sacs in some cases of their pneumonia series and stated that clinically they were cases of "asphyxia neonatorum." Since similar lesions had been found after inhalation of war gases and, experimentally, after intrabronchial insufflation of hydrochloric acid, they thought that this lesion also might be due to the aspiration of an irritating substance.

They injected lysol and soap, agents sometimes used in lubricating the vagina, intratracheally in rabbits but could not produce the typical lesions found in infant lungs. They finally concluded that the material composing the hyaline membrane in infant lungs was derived from epidermal cells and fat aspirated with amniotic fluid, probably some times previous to labor. They were unable however, to produce such membranes by experimental introduction of amniotic fluid into the lungs of rabbits. Farber and Sweet noted these membranes and believed that they were formed by vernix caseosa which had become compressed against the walls of the alveolar ducts and bronchioles. A similar membrane found in influenzal pneumonia was thought by Goodpasture¹⁰ to consist in part of fused necrotic mononuclear cells.

In the present study these membranes were not found in cases of pneumonia and were often observed in cases in which no amniotic sac contents were found so that infection and the constituents of amniotic fluid can be eliminated as the causes of their production. On the other hand they were usually associated with marked fatty and granular degeneration and desquamation of bronchial epithelial cells. Fat in fine droplets could be demonstrated in the degenerating cells and in the necrotic hyaline material which the writer believes to be the result of this degenerative process.

The subject of 'congenital' pneumonia has in recent years received considerable attention. The significant rôle that aspirated infected amniotic fluid plays in the etiology of antenatal and postnatal pneumonia was first stressed by Thaysen.² Thaysen found 8 per cent pneumonia in one series of forty nine and 42 per cent pneumonia in a later group of thirty two cases. Browne⁴ found pneumonia in 26 per cent of eighty autopsies and also believed that most of the cases of pneumonia in the first few days of life were due to aspiration of infected amniotic fluid. Johnson and Meyer⁵ in a study of 500 consecutive autopsies on stillborn or newborn infants reported 19.4 per cent pneumonia cases, and they also indicted aspiration of infected amniotic fluid. Cruickshank¹¹ found pneumonia in 25 per cent of his series of 800 infants who died during the first month of life. He believes that the presence of amniotic fluid may predispose to the development of pneumonia. A study of 240 consecutive autopsies upon infants, stillborn or dying during the first two weeks of life was recently reported by Warwick, who found evidence of pneumonia in 18 per cent of the cases, but she was uncertain whether bacteria or irritating amniotic fluid was the etiologic factor involved. Ten or almost 25 per cent of her series, were stillborn.

In the series of 100 cases reported here only six cases, or 6 per cent showed pneumonia and only one case occurred in a stillborn infant. In a number of the cases which histologically showed the lesions of

desquamative anaeriosis" a few red blood cells and leucocytes were found enmeshed with the desquamated cells. These cellular elements of the blood which escaped from the ruptured vessels of the loose, markedly edematous submucosa mixed with degenerated epithelial cells at times resemble an inflammatory exudate. It was also difficult to distinguish the early stages of active inflammatory hyperemia from the mechanical congestion unless a local leucocytosis was present.

The percentage of cases interpreted as pneumonia might well have been much higher had the diagnosis been made from the study of hematoxylin and eosin sections alone, but the Gram stain revealed no fibrin or bacteria in these pseudopneumonia cases. With the aid of the Gram and Giemsa stains, a number of cases which belonged in the "desquamative anaeriosis" group were thus properly classified as of noninflammatory origin.

The fact that amniotic sac contents were absent or present only in very small quantities in 83 per cent of the cases would indicate that the amniotic fluid itself was not the causative factor of the pneumonia. On the other hand, the presence of bacteria in 83 per cent of the cases indicates the important rôle of bacteria as the exciting factor in these cases. The presence of anatomic lesions of asphyxia and pneumonia in the same cases points to an intimate relationship between intrauterine asphyxia and bacterial invasion. Since bacteria were found only in those infants who died after one to fourteen days and in none of the stillborn infants, it is reasonable to surmise that infection took place at least in some of the cases after birth and not in utero. In a series of infants who lived from two hours to five weeks, Farber and Sweet² found that the cornified cells excited extraordinarily little reaction in the lungs, and no polymorphonuclear infiltration was noted except in the instances where infection was also present. Johnson and Meyer injected amniotic fluid into the air passages of rats but were unable to produce pneumonia. It therefore seems unwise to attempt to draw any inference as to the cause of pneumonia in our single case occurring in a stillborn infant that was associated with the presence of considerable quantities of amniotic fluid. This finding merely stresses again the close relationship between intrauterine asphyxia and "congenital" pneumonia. From my study one might conclude that pneumonia of the newborn is not a common finding, but that when it does occur it is usually superimposed on some degree of asphyxia.

SUMMARY

In a series of 100 consecutive autopsies on stillborn and newborn infants, anatomic lesions of intrauterine asphyxia were found in 80 per cent of the cases.

The pulmonary lesions found in these eighty cases have been described under the following headings:

- 1 Aspiration of large quantities of amniotic sac contents (11 per cent)
- 2 Marked desquamation of bronchial epithelium for which the name 'desquamative anaerobiosis' is proposed (31 per cent)
- 3 Congenital pneumonia (6 per cent)

Atelectasis was not a prominent feature in this series of cases.

The relationship of these lesions to asphyxia has been discussed, and the origin of the hyaline membrane seen in the bronchioles in certain of these conditions has been considered.

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GONORRHEAL VAGINITIS IN CHILDREN TREATED BY DIATHERMY

ONE- TO THREE-YEAR FOLLOW-UP

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MY PURPOSE in presenting this small series of cases is twofold: first, to show follow-up findings in this disease which extended in some cases over a period of three and a half years, and second, to compare the results obtained by diathermy with the results obtained by other more commonly used methods.

Four years ago I became interested in a group of children suffering from gonorrheal vaginitis, who had been treated at the Out-Patient Department of St. Luke's Hospital for periods varying from one to two years. The usual treatment of vaginal instillations of 5 per cent mercurochrome once a week was being used. This stopped the discharge temporarily, and the vaginal smear would become negative, but when the treatments were discontinued, the discharge recurred and the smears would again become positive. In going over the literature in an attempt to find a treatment method which would give a high percentage of permanent results, I was impressed by the work of Cumberbatch¹ of the St. Bartholomew's Hospital, London. He reported excellent results in cases in which diathermy had been used. At that time I thought that it would be worth while to follow carefully a small group of cases over several years in order to check on the permanency of the results.

In January, 1930, we treated our first case, and the last follow-up examination was in October, 1933. During this time we were able to follow fifteen children with gonocoeal vaginitis.

Method of Diagnosis—There is much controversy in the literature on the methods of diagnosis of gonocoeal vaginitis. In this series only patients are reported who had positive gonorrhea as judged by the criteria of Neisser, namely (a) demonstration of typical gram-negative diplococci within the leucocytes of the stained exudate and (b) inability to cultivate the organism on plain agar or gelatin. In some cases this cultural diagnosis was checked by obtaining a growth on modified Muslow's medium. The diagnosis was made by the St. Luke's Laboratory in cases there and by the City Hospital Laboratory for the cases in the foundling home. One case followed two years is not included because the laboratory failed to confirm a diagnosis made previously at another hospital.

Principle of Treatment—The principle of treatment has been outlined by Chamberbatch in his book on diathermy. He states, 'In all the cases (of gonorrheal vaginitis) which have been kept under observation, some for a year or more, the results have been permanent

The use of diathermy for the elimination of gonococci from the tissues is a rational procedure. In the first place the temperature which will kill the organisms is not high enough to damage the tissues. In the second place, the power of the tissues to eradicate infection is increased by heat. In the third place, the heat generated by diathermy current is not localized to the surface but distributed throughout the infected tissue.

The action of diathermy on infection is both direct and indirect. In the former the vitality of the organism is lowered or destroyed, in the latter the power of the tissues to eliminate them is increased. It is highly probable that the indirect action is more potent than the direct. Organisms with high lethal temperatures can be destroyed by diathermy without exceeding a temperature that will harm the tissues. Further it is possible to terminate gonococcal infection by heating the tissues to temperatures which are lower, and for times which are shorter than those found necessary in experiments on cultures.

Wertheim demonstrated gonococci beyond the epithelial layer in certain areas they were imbedded deep in the connective tissue. He made sections from the bladder of a child who died while suffering from gonococcal vaginitis and found gonococci between the epithelial cells extending into the subepithelial connective tissue. He also found them in the bladder and vaginal walls.

This would seem to show the folly of using local antiseptics which cannot penetrate deeply and the necessity of using a means of raising tissue resistance.

Technic of Treatment—The problem of obtaining the cooperation necessary for diathermy treatments in small children was the one most difficult to solve, and it was only by the patient persistence of Miss Reilly, head of the Physiotherapy Department of St. Luke's Hospital, and Miss Dalrymple nurse in charge of treatment at the foundling home, that we were able to succeed. The matter of getting the child's confidence was a delicate one. As a rule, no treatment was given at the first visit. A smear and culture were made and the child was allowed to play with the equipment which was to be used. At the next visit the electrodes were applied, but the current was not turned on usually by the third visit the actual treatment could be started.

For the inactive electrode a piece of moistened sheet tin, 3 inches by 4 inches, was placed just above the symphysis. A Corbus electrode, containing a thermometer was used as the active electrode in the vagina

There was no trouble in inserting this even in very young babies. The electrode temperature was gradually raised to 112° F and maintained at this level for a period of twenty minutes.

The patients in the acute group at the foundling home were given daily treatments, while the ambulatory patients in the chronic group were treated two or three times a week, depending upon their response to treatment.

In several of the cases in the acute group the smears and cultures continued to contain staphylococci. In some of these cases staphylogel, and in others pyridium, was used in conjunction with diathermy to destroy the staphylococci in the vaginal secretions. These surface antiseptics, except in one case, were used only after the smear had been negative for gonococci. In the one case the pyridium suppository in conjunction with the diathermy was successful in giving a consistently negative smear.

Results of Treatment—Of the fifteen patients whom we were able to follow, ten occurred during an epidemic of acute gonococcal vaginitis in a foundling home while the other five were chronic cases from the Out-Patient Department of St Luke's Hospital. The acute group and the chronic group are discussed separately.

In the acute series the ages varied from two months to twenty-two months. There was an accidental reinfection of the whole group in this series because of faulty technique on the part of the nurse in charge. This misfortune occurred two months after treatment had been started. At this time the vaginal smears on nine of the ten infants showed only a few pus cells and occasional extracellular gram-negative diplococci with a morphology of gonococci.

These cases were followed for periods varying from nine to thirty months, with the exception of one child who died of tuberculous meningitis three months after being discharged cured.

The time elapsing from the first treatment to the first negative smear averaged 16.2 weeks. This was not a fair test, however, on account of the accidental reinfection referred to, which made additional treatments necessary. The average total number of weeks until the smears were consistently negative was 21.6 weeks. After infection, the time elapsing until a consistently negative smear was obtained was found to average 13.1 weeks.

In the chronic cases the ages varied from one to nine years. These cases with the exception of one were followed for periods varying from one and a half to three and a half years. One case we were able to follow only three months after a consistently negative smear. One case had been treated in the clinic with mercuriochrome for twelve months and still had a positive smear.

TABLE I
DIATHERMY RESULTS

Average treatment time required till consistently negative smears	Acute Chronic	10 cases 5 cases	21.6 wk 4.6 wk
Percentage of consistently negative smears in series as of final visit	Acute Chronic	10 cases 5 cases	100% 100%
Time required for cure including treatment	Acute Chronic	10 cases *4 cases	9.30 mo 12-42 mo
Average time followed after consistently negative smears	Acute Chronic	10 cases *4 cases	12½ mo 33½ mo

One case could only be followed three months after a consistently negative smear

NUMBER OF WEEKS TILL FIRST NEGATIVE SMEAR				NUMBER OF WEEKS TILL CONSISTENTLY NEGATIVE SMEAR	
Acute Cases	V D	16	Average 16.2 weeks	20	Average 21.0 weeks
	R M	20		20	
	M I	16		20	
	D C	26		21	
	S E	3		20	
	E W	24		20	
	R M	12		12	
	K S	11		20	
	J Mc	20		25	
	J S	20		20	
Chronic Cases	A B	4	Average 4.2 weeks	4	Average 4.6 weeks
	B L	6		6	
	J W	6		6	
	E S	4		0	
	J P	1		1	

The time from the first treatment to the first negative smear averaged 4.2 weeks. The total number of weeks until the first consistently negative smear averaged 4.6 weeks.

The difference in the time required to clear up the chronic cases in comparison to the acute cases is noteworthy. Treatment in the chronic group seldom extended over two months, while in the acute cases, especially if the condition was present in babies under a year of age, a much longer time was needed for cure. The question arises if perhaps it would not be wise to delay diathermy treatment six weeks in acute cases, or until the body develops some resistance, so as to cut down the number of diathermy treatments.

Comparison With the Results of Other Treatments—In the *Hospital Social Service Supplement*, No. 1, March, 1933, is a comprehensive report, "Cervico-Vaginitis of Gonococcal Origin in Children." In this excellent summary of the medical and social angles of the problem, the following treatment methods were tried: mercurochrome, 2 per cent, as vaginal instillations, combined vaccines, acriflavine as vaginal instillations, and various combinations of these methods. The statement is made that the newer treatments, such as diathermy, have as yet not

proved of any greater value than the other time-tried methods. A control group was run in this series, and this group received no intravaginal treatment.

We quote from their "Main Findings and Recommendations" "Treatment as tested did not abort the disease. Its course was somewhat shortened by use of instillations of mercuriochrome in a 2 per cent aqueous solution applied daily at home, and by mercuriochrome in gelatin applied through the endoscope in the clinic. The obstinate character of this disease and its slow subsidence are confirmed. The disease is self-limited and usually fades out within a few months." This paradoxical statement is made in spite of the fact that in their own statistical tables they show that 37.9 per cent of their patients had had the infection for over a year and some had had it for seven years and over.

A chart of their twenty-six acute cases, in which the smear was positive and in which the mercuriochrome treatment was used, is found opposite page 34 of the report. An analysis of this chart shows that only sixteen cases had been followed more than a year after treatment was instituted. Of these, nine were treated fifteen months or less, four were treated from fifteen to eighteen months, and three were still being treated after eighteen to twenty months. At the end of a year, four of the sixteen still had positive smears, eight were doubtful, and only four had more than three consecutive negative smears.

A perusal of the results in the twenty-six cases shows that at the end of the twenty-month period six of the patients still had positive smears, five smears, doubtful, eight had less than three consecutive negative smears, and only seven had three consecutive smears and were considered cured.

In percentage, 26 per cent were cured (no mention is made of follow-up to see if they remained negative), 42 per cent were still positive or doubtful, and 30 per cent had less than three consecutive negative smears.

In their series of chronic cases, there were only fourteen with positive smears. Eight of these were treated for a period extending over a year, five were treated fifteen months, and one, seventeen months. According to the chart, at the end of the seventeen-month period there were three cases still positive, five had doubtful smears, five had less than three consecutive negative smears, and only one was cured.

In percentage this would be 7 per cent cured, i.e., three consecutive negative smears, 35 per cent with less than three consecutive negative smears, and 58 per cent still positive or suspicious.

In the control series in which no treatment was used, there were twenty acute cases with positive smears. At the end of thirty months eight were still positive, ten were doubtful, and only two were negative. In the chronic control cases there were only two with positive smears, and

these were negative at the end of the thirty month period. These items from the tables in the same report disprove the statement that this disease 'is self limited and usually fades out in a few months' and also correct the impression that 'old tried methods' are superior to diathermy

SUMMARY

1. Gonococcal vaginitis in children is not a self limited disease which tends to fade out in a few months as has been claimed. Statistics quoted from the article in which this statement is made show that over 37 per cent of the patients in that series had the disease for over a year and that one was supposed to have had it for seven years.

2. Theoretically, diathermy has an advantage over locally applied antiseptics in that it raises resistance in the tissues themselves enabling the body to destroy gonococci deep in the tissues

3. Practically, in actual results the diathermy patients had consistently negative smears after twenty nine weeks in the acute series and these remained negative during a follow up period which extended in some of the cases to twenty five months

4. The average length of treatment required to give consistently negative smears in the chronic cases was a little over four weeks. The longest follow up in this group was three and one half years.

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CONTINUOUS INTRAVENOUS THERAPY IN INFANTS

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THE importance of the continuous intravenous administration of various solutions has long been recognized, and its use, widely advocated. A study of the literature reveals that surgeons and pediatricians have taken the lead in evolving methods and techniques intended to overcome the obstacles encountered in this type of therapy. Until recently, surgeons have been far ahead in its use, because of the technical difficulties encountered in its use in infants by pediatricians. A German surgeon¹ writes of "twenty years experience in the use of continuous intravenous infusions." Matas,² who used it in postoperative cases, is given credit for introduction of this type of treatment into this country. In the past three years many workers have published the result of their experience. All agree that the procedure is of special benefit in selected pediatric cases, that its use should be more widespread, and that no other therapy is so efficient or acts as quickly.

In 1930, Hendon³ wrote of this treatment, naming it "venoclysis", Horsley and Horsley⁴ in 1931 introduced a new intravenous cannula, Karchitz,⁵ using continuous dextrose infusions in twenty-one cases of toxicosis, reported excellent results and later with Schick⁶ reported on its use in treating fifty-three cases of alimentary toxicosis. Hyman and Hirshfeld⁷ at first used dextrose solutions and later⁸ added blood, various serums, antitoxins, and drugs, such as caffeine and epinephrine in cases of shock, hemorrhage, infection, surgical procedures, and thyrotoxicosis. Stokes⁹ concluded that venoclysis has an important place in pediatric therapeutics in combating serious ketosis and stimulating the kidney to a greater functional activity. Bier¹⁰ summed up the advantages of intravenous therapy as assuring accuracy of dosage, allowing ease of administration, giving maximum action in minimum time, and providing more definite results. Brush¹¹ presented a new method for intravenous infusions in infants by which he attempted to overcome most of the difficulties encountered. Cohen and his coworkers¹² made a comprehensive study of the changes in acid-base equilibrium brought about by intravenous drip and concluded that dehydration is rapidly corrected, that diuresis is reestablished, that nonprotein nitrogen retention in the blood is lessened, and that clinical improvement usually precedes chemical readjustment. Nesbit¹³ pointed out the necessity of changing the picture

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of toxemia found in upper intestinal tract obstruction in infants before the necessary surgery is instituted, he stated that this is best accomplished by the absolute rest of the gastrointestinal tract afforded by intravenous therapy

INDICATIONS

The indications for the use of the continuous intravenous therapy in our practice are those of the loss of or need of body fluids. Dehydration and acidosis are relatively common in many diseases encountered in pediatric practice, particularly in the South during the summer months. The various diarrheas, cholera infantum, alimentary intoxication, cyclic vomiting, and vomiting with acute infections—the toxemia accompanying such conditions as otitis media, pneumonia, dysentery, burns, pyelitis, and merasmus—the postoperative need of fluids as encountered in intussusception, pyloric stenosis, intestinal obstruction, and peritonitis—all give the pediatrician ample opportunity for the use of treatment calculated to replenish safely lost blood volume, to overcome lack of tissue fluids, and to prevent anhydremia, while at the same time providing for rapid elimination of by products of the infections and preventing the dread anuria.

We have frequently found the introduction of fluids by hypodermoclysis to be inadequate or poorly absorbed. Intraperitoneal fluids may be contraindicated because of an abdominal operation or presence of a large amount of gas in the bowel in patients with respiratory embarrassment such as is frequently encountered in pneumonia. Proctoclysis is a well known failure in infants. All of these methods are accompanied by discomfort or pain and are undoubtedly a strain on the strength of the infant. We have noted with Cohen¹² and others that continuous intravenous administration is, in the great majority of cases, accompanied by quieting of the patient and affording needed rest.

SOLUTIONS

It is not the purpose of this paper to discuss the effect of the administration of various solutions on the blood constituents and body tissues or on the toxic products caused by infection. It is sufficient to say that almost every solution, drug, serum, or antitoxin ever given by vein has been administered as part of continuous venoclysis. Included in this list is the intravenous use of diphtheria antitoxin, magnesium sulphate in cerebral edema, calcium chloride and acacia in nephritic edema, neoarsphenamine, tetanus antitoxin, gentian violet and mercurchrome in septicemia, and typhoid vaccine in chorea.

Our experience is limited to five solutions

1 Dilute glucose solutions, usually from 5 to 10 per cent dextrose. This is our solution of choice because of its safety in either alkalosis

or acidosis and because it furnishes nutrition as well as fluid. This is especially advantageous when adequate feeding by mouth is difficult or impossible.

2 Physiological salt solution

3 Hartmann's¹⁴ solution, which is of particular advantage when loss of minerals is evident as in the diarrheas.

4 Molar sodium lactate, as advocated by Marriott¹⁵ in the treatment of systemic disturbances associated with diarrhea.

5 Occasional infusions of 4 per cent soda bicarbonate solutions in severe acidosis and persistent pyelitis.

We have not attempted to give blood or serum by this method as it would not be feasible with the small needle we use. We have not used stimulants, such as caffeine and epinephrine, because of the belief that the drug would be too dilute to be of value. We have not added various serums and antitoxins to the solutions. We note that this view is shared by others and the prevalent tendency is to limit continuous intravenous drips to dextrose solutions and solutions containing minerals, such as normal saline or Hartmann's solution. Neither do we advocate the therapy for use in too many conditions, our use having been limited to critically ill patients suffering from lack of fluid. Marriott¹⁵ has shown that complete rest of the bowel in diarrheal conditions can only be accomplished by affording needed nutrition through other channels than the mouth and that this rest of the bowel is considered the most important single factor in treatment. It must be remembered that intravenous infusions are only a part of the scheme of treatment, which must be instituted for the patient. Starvation, medication, removal of foci of infection, diet, and other therapy of choice must be provided.

Our statements concerning the use of this procedure are based on its use in 511 cases. During the summer of 1933, in dealing with cases of parenteral and fermentative diarrhea, dysentery, typhoid, and paratyphoid fevers, we averaged from eighty to ninety intravenous drips per month. In such a large number of severely ill patients, we were naturally able to depend on the clinical picture only, and we were distinctly impressed by the rapidity in the change of condition of many of these infants.

It would seem that little could be added to a therapy already investigated from so many angles, but may we point out that in the reports of all authors quoted and in all other reports we have been able to find, the site of choice for the administration of the continuous intravenous drip was a dissected vein, either in the cubital fossa or more often the saphenous vein of the leg, and that various types of cannulas, catheters, and large needles were inserted. In all of our injections we used a very small needle inserted in a small vein. In one of our cases we gave seventeen separate intravenous drips, exclusive of blood trans-

fusions, over a six week period of time. May we ask the question, "Could this have been done had our method necessitated cutting down on the vein each time?"

SITE OF CHOICE

For some time before we began using the continuous intravenous drip, we gave all blood transfusions in small capillaries and venules on the back of the hand, dorsum of the foot, and most commonly, over the scalp. The scalp is by far the most logical choice in the continuous administration of a solution in the vein because (1) the blood vessel is stable, (2) the application is easy, (3) the patient may move or toss the head, the arms and legs being free, and (4) the vessels in this area are the smallest. The last reason is important, as it is our contention that the greatest difficulty in the use of continuous intravenous administration, i.e., clogging of the needle or cannula by blood, is thus overcome. The pressure within the large vein is enough to force a small amount of blood back into the apparatus and after a few hours obstruction is the rule. We have found that on extremely small vessels approximately the size of the needle will both accommodate the flow and prevent blocking of the needle. It is as easy to insert a small needle into a small vein as a cannula into a large vein.

There are other logical reasons for choosing this site. It does not offer the danger encountered in injections into the superior longitudinal sinus, into which injections should not be made by other than an expert, it does not offer the possibility of a hematoma with resulting infection and necrosis of tissue as sometimes is seen in jugular vein injections, it removes the chance of infection taken in cutting down on a vein. It is almost painless and therefore saves the strength of the already weakened infant. In short, there are relatively no dangers in the method, and it may be done at the bedside.

In looking closely at the scalp, we find many small tributaries of the superficial temporal veins draining the parietal and frontal aspects of the scalp in addition to the two or three small tributaries of the frontal and supraorbital veins, which drain the anterior part of the scalp and flow down over the middle of the forehead. The latter vessels are our first choice, because the child can roll his head from side to side without interfering with the flow of the solution. Shoving the head allows the operator to find these veins more easily.

APPARATUS

The apparatus, with the exception of the needle, has been used many times by others. The infusion is given entirely by gravity. The container is an ordinary 300 c.c. salvarsan tube connected by a short piece of rubber tubing to a drip bulb commonly known as the Murphy drip, from which a piece of rubber tubing, from 3 to 4 feet in length passes

to a small glass adapter $\frac{1}{2}$ inch in length. The needle, a 28 gauge one-half inch so-called tuberculin needle, smaller than the ordinary hypodermic needle, fits the adapter. It is easy to see that this is a very simple and inexpensive apparatus. The container hangs on the hook of a standard, adjustable in height. This adjustability regulates the rate of flow, which also may be regulated by a screw clamp inserted anywhere between the drip bulb and the needle. After trying several methods of keeping the needle in the vein, we found the simplest and most efficient aid is a 3-inch strip of adhesive tape, 2 inches wide. This is placed firmly over the needle, adapter, and skin directly in front of the needle. A small piece of cotton is placed under the adapter. In case of movement of the scalp, the skin, vein, and needle move together, without disturbing the flow. Such procedures as examination of the ears, mouth, and throat may be carried on without dislodging the needle.

RATE OF FLOW

We have found that the rate of flow is best regulated by raising or lowering the height of the column of solution, there is a possibility of entirely shutting off the flow if the screw clamp is used. The rate of flow is judged by the number of drops per minute, this varies from 5 to 30 drops, the latter being about as fast as the tiny needle will permit passage of the fluid from a column height of three to four feet. The first 200 or 300 c c are allowed to enter the vein at a rate of 15 to 20 drops per minute, or from 60 to 80 c c per hour, then the rate of flow is usually reduced to 10 or 12 drops per minute and regulated according to the heart rate, the beginning of diuresis, and the clinical appearance of the patient.

TEMPERATURE

The temperature of the solution is not a very important matter. Ordinary room temperature is regarded as safe, but it is our common practice to keep a hot water bag around the container or circling the tubing. The remarkable absence of any untoward reactions to the drip testify as to its margin of safety. We have found that it is best to have the needle sharp with a long bevel. The most common error is inserting the needle too deeply. Frequently the bevel of the needle can be seen intracutaneously while the solution is flowing.

BLOOD TRANSFUSIONS

Blood transfusions are given in the same small blood vessels with the same sized needle. Our transfusion apparatus does not include the drip bulb, but a three-way stopcock is inserted. The blood is drawn from the salvarsan tube into a syringe fitting the stopcock, the valve is turned and the blood injected into the vein slowly. Citrated blood, which is strained when placed in the container, is used. Obstruction of

the needle is rare, but in case this happens the needle is withdrawn and another is slipped into the vein $\frac{1}{2}$ inch farther down its course. It is the rule for infants receiving transfusions by this method to sleep quietly throughout the procedure. Because of the benefits to the infant, we have adopted the scalp vein route for all intravenous medication.

SUMMARY

1 Continuous intravenous therapy is applicable to many conditions encountered in pediatrics.

2 Our use of this procedure in 511 cases convinces us of its value in indicated cases.

3 We present a method using the smallest scalp veins, the method is easily employed, without discomfort, pain, or danger to the infant.

4 If continuous intravenous drip is not desired, blood transfusions and all other intravenous injections may be given by way of the veins of the scalp.

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HYDROCEPHALUS OF UNUSUAL SIZE

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HYDROCEPHALUS, or progressive enlargement of the cranium with general enfeeblement, occurring in infancy and early childhood, is prevalent enough to have been observed by almost every physician at one time or another. However, it is very rarely that we have occasion to see those unfortunate patients whose heads are of astoundingly huge dimensions. It is the purpose therefore, merely to present a case of this sort, which reveals cranial measurements of unusual magnitude for a child of her age.

CASE REPORT

L. J., a fifteen month old white female child, was brought to the hospital Feb. 2, 1934, because of progressive enlargement of the skull. The family history was entirely negative. She was the first born, a normally delivered, full term baby. At the time of birth a cystic mass was noted at the level of the lumbodorsal spine. This condition was considered to be spina bifida with a meningocele. When the baby was four days old, operation, consisting of complete removal of the mass, was performed and confirmed the diagnosis. The child made an uneventful recovery, the wound healing by primary union. However, the parents were cautioned to measure the head at regular intervals and to note any too rapid increase in size. For seven weeks the baby did remarkably well, her development and functions being perfectly normal. It was at this age that the cranium began to show evidences of cerebrospinal fluid accumulation. The head became progressively larger and the mental status gradually waned until at the time of admission the head was enormous and the child a total mental deficient.

Physical examination revealed a very well nourished child who was a profound defective and obviously amaurotic. When the infant reacted to pain and temperature stimulation, the cry was that of a normal baby of this age. The head was about the size of a large pumpkin and presented the following measurements:

	CIRCUMFERENCE		DIAMETER	
	CM	IN	CM	IN
Occipitofrontal	92	36.6	30	12.5
Suboccipitobregmatic	87	35	26	10.5
Suboccipitofrontal	82	33	25	10
Biparietal	—	—	28.7	11.5
Anterior fontanel	20 × 21 cm			
Posterior fontanel	11 × 11 cm			

The subcutaneous veins of the scalp were markedly distended and at either parietal region was an extensive area of ulceration, which was probably due to pressure from so great a weight of encapsulated fluid. Obviously, the child was unable to move

From the service of Dr. Louis H. Barenberg, Department of Pediatrics, Morrisania City Hospital, New York City.

its head. The frontal bosses were overhanging and the eyes, therefore, appeared depressed. The internal ophthalmi were markedly distorted because of the lifting of the scalp. The sclerae were bluish and a coarse perpetual nystagmus was noted. The pupils were equally and evenly dilated and revealed a clear media. No circulatory disturbance of the retinae was visualized, but the optic discs appeared pearly white. The ears and nose were normal, as were the chest and abdomen. At the lumbodorsal level of the spine was a nicely healed scar of the operation. Scattered over the vulva and buttocks were several areas of excoriation. The extremities presented a spastic tetraparesis with absence of reflexes.

The laboratory findings were all negative. The urine was normal repeatedly throughout the course of life. The Schick and Mantoux tests were negative as was the Wassermann reaction. The hemogram follows:



FIG. 1.

Hemoglobin	76 per cent (Bahl)
Red blood cells	4,400,000
White blood cells	10,700
Differential	polymorphonuclears 76%
	eosinophils 2%
	lymphocytes 20%
	monocytes 2%
Smears—normal	
Calcium	10.0 mg per 100 c.c. blood
Phosphorus	4.2 mg per 100 c.c. blood

Puncture of the spine and cisterna magna revealed 20 mm. of mercury pressure and following injection of methylene blue into the cisterna the dye appeared within a minute at the spinal needle which was introduced below the level of the operation.

Radiographic examination of the skull disclosed it to be tremendous in size. The cranium was absent throughout the entire extent except for a few thin portions along the vault, frontal, and occipital regions. The sella turcica could not be definitely visualized because of the enormous quantity of fluid.

The child's course, of about six weeks in the hospital, was uneventful until a few days before death, when she developed a bronchopneumonia. During the interim

she had neither gastrointestinal nor cardiorespiratory disturbances. The intercurrent infection was moderately severe and in three days she died.

Necropsy

The calvarium was composed of relatively small amounts of bone. The dura was easily separated, revealing a soft, tense cerebral surface on which the blood vessels stood out very prominently. The convolutions were completely flattened. The brain tissue was very friable and varied from $\frac{1}{4}$ to $\frac{1}{2}$ in. in thickness, being thinnest at its vertex. The cerebral surface was punctured and 375 oz (11,250 cc) of a clear, colorless cerebrospinal fluid was obtained. With its removal, the shell of brain tissue collapsed. Aside from this thin shell of cerebrum, no other brain tissue was present excepting the cerebellum and the pons.

The whole brain resembled a cystic sac about the size of a watermelon and presented an internal hydrocephalus. The spinal cord was also removed and showed a small opening at its lower end in the region of the fifth lumbar vertebra, which opening was covered over by a thin fibrous band.

The lungs were free in the pleural spaces. There was marked basal congestion. On section the base of the right lung was purplish in color and completely atelectatic. The base of the left lung showed areas of grayish infiltration which were lobular in distribution. The heart was normal.

When the abdomen was opened, a small excess of dark amber fluid was noted. The mesenteric glands were larger than normal, and the serosa of the intestine was somewhat injected. The liver showed cloudy swellings, and small areas of fatty vacuolization were seen. The spleen was enlarged and grayish red in color. Both kidneys were normal although the pelvis were dilated and the mucosa injected and granular. The remainder of the examination was entirely negative.

COMMENT

The case of hydrocephalus presented is probably one of congenital origin, but the question arises as to the relationship between the removal of the meningocele and the production or presence of the excessive cerebrospinal fluid. It is the common belief that excision of a meningocele stimulates the production, or is followed, by a "water head." Whether the removal of so small a portion of the arachnoid, in other words, reabsorbing surface for cerebrospinal fluid, is sufficient to cause an imbalance between production and absorption of the fluid is still an open question. Dandy¹ says "Hydrocephalus frequently develops after removal of such a lesion, particularly the spinal meningocele, but doubtless its disclosure is purely incidental. Hydrocephalus, if it later develops, was unquestionably progressing when the meningocele was removed but had not yet given evidence of its presence by enlargement of the head."

It is amazing that in cases of such tremendous size, in which the brain has become so markedly distended, as in this case, function still persists. There is, of course, less compression in infancy, in as much as the open sutures, fontanelles, and soft bones yield more readily to the progressive expansion.

Holt suggested that if the head grows more than one inch a month, there can be little doubt of hydrocephalus. These cases of congenital hydrocephalus only rarely exist beyond one year of age. At any early stage of the disease it may become arrested spontaneously and the patient attain adult life, but in most cases it is progressive, and death occurs either through inanition or some intercurrent infection.

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Pediatric Clinics

THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET, LONDON

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IN THE middle of last century Dr Charles West, a well known and philanthropic physician, with various friends to help him including Sir Henry Bence Jones, an eminent physician of the day, having decided that the conditions under which sick children were treated in London fell far short of what should be, determined to start a hospital entirely for children. A commodious old house in Great Ormond Street, once the home of Dr Mead, Physician to the Court of Queen Anne, was acquired, adapted, and opened in 1852, with ten beds. The president was the famous Lord Shaftesbury, and it may be said that right from those early days the Hospital has always attracted the services on the lay side of distinguished men and women. Charles Dickens was a warm supporter of its work, and today H R H the Prince of Wales is the keen holder of the presidential position.

The ten beds soon proved inadequate. Adjoining houses were purchased, but these, too, proved insufficient. By 1860 the annual number of in patients was 384, and out patients, 8,800. In ten years there was another big increase, and adjoining land was purchased so that the first buildings specially designed as a hospital unit could be created. These buildings and wards of the '70's form to this day the main block of the Hospital. Still the work grew, and in 1893 the new South Block was opened with due ceremony by the Prince and Princess of Wales (afterwards King Edward and Queen Alexandra) who had always shown a keen interest in the Hospital. Ten years later the first Lord Astor most generously gave an entirely new and up to date out patient department in memory of his daughter. Then two adjoining early eighteenth century houses were acquired as accommodation for nurses, and finally, a few years ago, the first part of the great new reconstruction scheme was launched with the erection and completion this year of a new nurses' home on the north of the present site. It is planned to build the whole hospital in the course of the next few years in accordance with modern needs, for it must be realized that buildings dating from the 1870's leave much to be desired as regards equipment and accommodation.

This brief sketch of the Hospital's bricks and stones, however, is only part of its history. Great Ormond Street has become known all over the world because of the work it has done in the field of paediatrics. Those of us who, as junior members of the staff, can look forward to the new buildings are mindful of the fact that in these old wards and laboratories was laid the foundation of modern knowledge of many disorders. Sir William Jenner, for example, did much to elucidate the mysteries of rickets, and he pointed out the lines of its successful treatment long before vitamin D was discovered. It was in the old wards, too, that Cheadle clearly recognized the nature of infantile scurvy and established the method of treatment still in vogue. Sir Thomas Barlow followed this with his classical investigation into the

*Physician to the Out-Patients at the Hospital

pathology of the disease, and the pathologic museum today contains the original specimens upon which Barlow based those conclusions which have resulted in his name being attached to infantile scurvy all over the world. Also in the old building was worked out the pathology and clinical features of Still's disease and also by Still, the bacteriology of posthæmic meningitis. On the surgical side, Sir William Arbuthnot Lane performed many of his famous operations in this hospital, Sir Charles Ballance carried out his pioneer work on mastoid disease, and Mr Wagh devised his method of removing tonsils by dissection, which has spread all over the world.

The Hospital undertakes a vast volume of work. More than 7 000 in patients pass through the service each year while new out patients number annually 32 000, entail



The Hospital for Sick Children, Great Ormond Street

ing over 110,000 attendances or between three and four hundred children every working day. The main building has 252 beds, mostly in eight large wards, four for medical and four for surgical cases. Isolation wards also exist including a complete and separate unit for the treatment of venereal disease, but there are no special wards for babies, each main ward taking a limited proportion of children under two years. There are in addition seventy-five beds at the Country Branch of the Hospital at Tadworth, Surrey (near the famous race-course where the Derby is run) and it is proposed to increase gradually the number of beds in this convalescent section. There are pathologic, research, biochemical, and electrical departments at the main hospital, a library (containing many old books on paediatrics) and a museum full of historical specimens and up-to-date material. The out patient department comprises (1) a large casualty section with isolation rooms for the chief

infectious diseases and an operating theater for minor surgery, (2) the main Astor block with four complete sets of clinic rooms so that four separate members of the staff can work at once, with all the necessary ancillary services of social workers, massago, electrical, and other forms of treatment. Special clinics for child guidance, speech training, asthma, and rheumatism are also held.

The active Honorary Staff consists of four physicians, five physicians to out patients, six surgeons, a dermatologic physician, ophthalmic surgeon, dental surgeon, a radiologist, and four visiting anaesthetists. There is a director of the pathologic department, biochemist, assistant pathologist, and a research worker attached to this department. The junior staff comprises a resident medical superintendent, medical registrar and pathologist, two out patient medical registrars, three surgical registrars, a casualty medical officer, two resident house physicians, and two resident house surgeons, these last corresponding to the position of internes.

The Hospital is supported largely by voluntary contributions in addition to certain grants from central funds, payment by public health authorities for certain specific services, and payments made on behalf of patients according to the means of the parents. It is administered by a Board of Management on which, as has already been said, many distinguished friends of the Hospital have served.

The Medical School is under the direction of a dean, and under this organization is included the training of undergraduate students who come from the medical schools of London for definite periods and the whole of the postgraduate teaching which is going almost continuously throughout the year. The Hospital and Medical School are recognized by the various examining bodies including the Universities of Oxford, Cambridge, and London for undergraduate and postgraduate instruction. Such teaching and training is almost all carried out in the old tradition of Great Ormond Street, namely by clinical instruction in the ordinary routine course of the Hospital's work. Ward visits by the more senior members of the honorary staff and out patient clinics held daily supply a vast amount of varied clinical material. The Hospital by virtue of its unique historical position attracts patients from all over the world and difficult problems in diagnosis are particularly likely to find their way there. There are also from time to time special courses of lectures and demonstrations dealing with special subjects. The resident appointments are much sought after, young graduates from all over the British Isles and the Colonies actively compete for the six months of office which is regarded as a valuable training. One result of this is that in many towns in the United Kingdom and British Empire the methods and traditions of Great Ormond Street are actively practised and passed on so that it is true to say that children benefit from the teaching of Great Ormond Street who have never been within a thousand miles of its doors.

Research work is partly carried out in special clinics organized for the purpose, as in the recent development of the rheumatism and asthma clinics where all the patients with these diseases are supervised by special investigating medical officers under direction of the visiting medical staff. Research work of a more pathologic nature is pursued by the holder of a special research fellowship, and in the new hospital under consideration it is hoped that it will be possible to provide more facilities for visiting research workers. The bulk of the research at Great Ormond Street has always been in the nature of "clinical research," and the observation of large number of cases of special disorders has yielded much fruit in relation to their correct treatment and management.

The training of nurses has always been a feature of the Hospital's work. One of Dr. Charles West's objects in founding the institution was to secure better nursing of the sick child and today the efficiency and skill of the nurses trained at Great Ormond Street is indicated by the great popularity of the private nursing staff, available and utilized for private nursing in every part of the kingdom. The nurses enter

as probationers and receive three years of extensive practical and theoretical training in the course of preparation for the state examinations for admission to the official Register of Sick Children's Nurses. There is a long waiting list of those who seek this training, and among the senior nurses many seek a further training at a general hospital in order to qualify for the post of "sister" to one of the wards at Great Ormond Street.

The social work of the Hospital, with the large number of in and out patients daily treated is obviously of great importance. The Hospital has six trained almoners, in addition to almoner students, who work in close cooperation with the medical staff. Each year convalescent treatment has to be arranged for over two thousand children in some of the many institutions available at the seaside or in the country. The supply of dental and surgical apparatus, the arrangement for massage and artificial sunlight treatment in local clinics when the patients live at some distance from the hospital, securing the services of district nurses to carry out home treatment and close cooperation with the education authorities, the public health authorities, and the special public assistance committees (for poor relief etc.) are also part of the social work. In this department also comes the machinery for the follow up of patients who have ceased to attend, necessitating sometimes the securing of special conveyances and escorts. Since the Hospital is largely supported as already said, by voluntary contributions for the benefit of the sick poor, it follows that one of the duties also undertaken by the almoner's department is to see that this primary object is not abused. The full facilities of the institution are freely available to all but those who can make some contribution, however small, are invited to do so.

The records of the Hospital go back to the time of its foundation. Some of Dr Charles West's original case notebooks now in the library, are full of detailed observations, and a fine set of postmortem registers contain pathologic descriptions of great value. The use of these records is frequently being sought by statistical research workers.

If there is a note of pride in this sketch (or to the reader a suspicion of boasting or vaingloriousness), that is because all who work in the Hospital for Sick Children, Great Ormond Street feel that way about their institution. The spirit of enthusiasm and hard work has come down to us from distinguished pioneers. We are proud to receive it and proud to pass it on. In the newly reconstructed Hospital we shall be proud to welcome visitors as we are now in the hope that they too, may capture something of the spirit which hangs about this particular part of a great city.

Critical Review

DISORDERS OF INTERNAL GLAND SECRETION IN CHILDREN

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IT IS unfortunate that terminology of the literature on the glands of internal secretion is so confusing that it is difficult in many instances to determine exactly what an author is writing about. This confusion and the mistakes which result from it has been greatly increased by the use of the coined names given to various extracts. This led to an editorial in the *Journal of the American Medical Association* (October 13, 1934, p 1152) in which it is urged that "short descriptive phrases" be used to designate the substance rather than "coined names" which include "synonyms (real and alleged) and trade-marks" as well as the "terms invented from time to time by research workers in many parts of the world." Under the group of estrogenic substances may be included "female sex hormones, estrin (oestrin), follicular hormone, folliculin, theelin (ketohydroxyestrin, estrone), theelol (follicular hormone hydrate, trihydroxyestrin, estriol)," and such trade names as "amniotin, progynon, emmenin and menformon." The only way to avoid the inevitable confusion is to designate the substance and its source for example, estrogenic substance in the blood, lactogenic factor of the anterior pituitary, follicle stimulating factor, luteinizing principle, et cetera.

The fallacy of assuming that because some effect is obtained in rats or rabbits the same thing will also happen in the human being has again been emphasized. Yet, it is clear that much ground has been covered to advantage and some of the doubtful points about the endocrine glands are less obscure.

Thyroxine—Anderson² reports the use of 3.5 diiodothyronine in doses of 50 to 75 mg daily in the treatment of high grade myxedema (presumably adults). He thinks that the drug, which can be obtained synthetically, becomes converted into thyroxine and says toxic symptoms have never been observed from its use. Thompson and his coworkers³⁰ found that the solubility of the thyroxine used was a factor in its absorption from the gastrointestinal tract and hence its effect on the basal metabolism. This is of practical importance to the clinician.

Lerman and Salter²² compared the relative calorogenic action of several preparations and found that the amounts of commercial thyroid preparations equivalent to 1 mg of thyroxin polypeptide or 0.75 mg of crystalline thyroxin were as given in Table I.

TABLE I

		GRAINS	GRAMS
Thyroxin Polypeptide 1 mg	Armour & Co Thyroid	3.3	0.22
	Lederle Laboratories, Inc, Thyroid	3.5	0.23
	Burroughs Wellcome Thyroid	10.2	0.68
	Parke, Davis & Co Thyroid	2.5	0.17

This data is very important to the clinician since it explains many inconsistencies in results and makes clear the necessity of recording in all records the make of thyroid used. Since the Parke, Davis & Co thyroid has a calorogenic activity four times greater than the Burroughs Wellcome product and almost one and one-half times greater than Lederle's and Armour's, it should be used in smaller doses to obtain the same effect.

Iodine—It has been found by various writers that the size of the thyroid gland and its iodine content varies with the seasons in different parts of the country. Low iodine content of the food predisposes to or causes, goiter. Goiter is even found in Holland, where one would naturally not expect it. Pennick²² found it especially prevalent in Utrecht. This was attributed to the increase in use of waters taken from the deep strata of the earth (presumably by means of artesian wells) which had a low iodine content.

Kolnitz and Remington²¹ made a study of human thyroid glands in South Carolina and found that the weight of the gland was smaller and the percentage of iodine higher than elsewhere. The "summer glands" were heavier and as a result had greater amounts of iodine because the percentage of iodine was practically constant.

Hamilton²³ studied the effect of various salts on the thyroid gland of rats. When they were fed on sodium fluoride, sodium chloride and calcium chloride, their thyroid gland showed normal histology, but rats fed on sodium iodide showed a flattened epithelium, while those fed on sodium bromide showed hyperemia, follicular degeneration, epithelial desquamation and disappearance of colloid. Hellwig¹⁸ on the other hand, was able to cause colloid goiter in seven rats with a diet high in calcium chloride when ten times the physiologic requirements of iodine was added.

Hyperthyroidism—Lahey²² considers that hyperthyroidism in children is a little more dangerous from the surgical point of view than intense hyperthyroidism in the young adult. Very young children, from three to five years of age he says should be operated in two stages because of excessive reactions. The danger of removing too much thyroid and thus affecting growth and development must be considered. If too much thyroid is removed therapy cannot completely replace the lacking gland. Too much emphasis cannot be laid on this possible danger, since lack of thyroid as seen in infants and young children often results in myxedema, with failure in growth and mental development, even with treatment.

The interrelationship of the thyroid and pituitary glands have been commented on before. Hertz and Krane²⁴ found involutional and atrophic changes in the thyroid glands of animals which had received large doses of pituitary materials for more than a week. These changes were involution and finally atrophy with marked colloid storage. Foster¹⁰ found a decreased iodine content after injection of a saline extract of the anterior lobe.

High cholesterol content of the blood is reported in hypothyroidism of childhood by Bronstein.⁹ Julius P. Hess²⁵ determined the blood cholesterol in twenty five children between the ages of two months and eleven years. The blood cholesterol level varied from 217 to 129 in these cases. In three children with hypothyroidism the cholesterol was respectively 454, 454, and 416. He also observed that the creatine

excretion in two female children with hypothyroidism was diminished or absent except when they received thyroid therapy or creatine by mouth. He feels that this data is useful in diagnosis in childhood.

Parathyroids—The knowledge of the parathyroid glands has developed and clarified markedly so that it is possible to state that hyperparathyroidism is usually due to an adenoma of the parathyroid gland. There results an increased production of parathyroid hormone and a disturbance in the calcium and phosphorus metabolism. This can be diagnosed by a high level of calcium in the blood, a decreased phosphorus, and an increased excretion of both calcium and phosphorus in the urine. It is thus easy to see why the bones can become demineralized and why, with such a large amount of these salts in the urine, urinary calculi may form.¹

Recent studies of the parathyroid have shown that its location varies.¹⁴ An analysis of the cases studied showed 7 per cent of the glands opposite the cranial third of the thyroid, 57 per cent, the middle third, 25.6 per cent, the caudal third, and 10.4 per cent were found caudal of the thymus gland. There were four parathyroids in 50 per cent of the patients. Brewer² reports four human cases with parathyroids in the thymus. Surgical removal, therefore, should only be attempted after a diagnosis is made in the laboratory, and the surgeon must be prepared to hunt for the gland in unexpected places.

Hertz and Kianes¹⁶ found that animals treated with anterior lobe extracts and pregnancy urine showed more vascular and grossly larger parathyroids than the control group. They showed histologic changes consistent with hypertrophy and hyperplasia. Parathyroid hormone was demonstrated by Hoffman¹⁹ in the blood of pregnant women after the third to fourth month. It was never found in nonpregnant women.

Pituitary Gland—The part played by pituitary gland in the endocrine system is assuming more and more importance. Its influence on the thyroid has been studied from various angles. The injection of alkaline or acid extracts of the anterior pituitary gland into animals has been shown by Hertz and Kianes¹⁷ to cause involution and finally atrophy of the thyroid when continued. This from Collip's⁸ point of view would suggest the development of some antistubstance which counteracted the injected material, but from the point of view of the authors it can be explained more reasonably if one infers that the overstimulation of the thyroid causes it to wear out prematurely. This seems to the writer the most plausible explanation.

Changes in the basal metabolism of hypophysectomized dogs were obtained by Houssay.²⁰ A lowered metabolism was found in these animals which was accompanied by morphologic changes in the thyroid characteristic of hypothyroidism. That this fall in the metabolism was due to the loss of the pituitary and not to changes in the thyroid alone was evidenced by a further fall in the metabolism after their thyroid was also removed. The injection of the thyrotropic hormone of the pituitary into three human subjects was followed, according to Eitel and Loeser,⁸ by an increase of the metabolism of 22 to 43 per cent.

Riddle and Bates²⁰ consider the unsatisfactory nature of tests of the growth hormone "is now the greatest single obstacle to further successful research on the functions and chemistry of the anterior pituitary gland." He finds that a gonad-stimulating hormone can induce growth of the mature testes or ovary beyond the normal size limits in the ring dove.

Engelbach and Schaefer³ found that libido and potentia disappeared when the growth hormone antuitrin G (Parke, Davis & Co. not available commercially) was administered to a thirty-four year old dwarf and concluded that there must be an antagonism between the sex and growth factors. They also reported growth induced by this hormone in children who had not grown during the previous three months. A study of the evidence is not very convincing because it covered too short a period and it is well known that growth in height can normally take place in some seasons of the year and be retarded or absent in others.

Pituitary Headache—It is not clear from Skipp's description²⁰ exactly what clinical symptoms represent pituitary headache, but he reports success in treating chronic recurrent headaches by injections of pituitrin and pituitrin tablets by mouth.

Undescended Testes—Sexton²¹ Colm,²² and Rubinstein²³ treated boys with undescended testes by means of the anterior pituitary like substance in pregnancy urine and obtained favorable results especially in fat boys. After longer and shorter periods of treatment the testicles of many of these subjects descended into the scrotum. If the results of this method of therapy are confirmed in future cases an important advance has been made in the treatment of these individuals.

Suprarenal Cortex—Evidence has been accumulating that there is a relationship between some of the vitamins and the suprarenal cortex.²⁴ The cortical extract was found to have no influence on avitaminosis A. The experiments showed that "either cortin or some unidentified substance aids in the utilization of vitamins C and B. Since cortical extract retards the onset of the avitaminosis symptoms of vitamins C and B, it is suggested that an ample supply of these vitamins would be advantageous in adrenal cortical insufficiency."

Freeman Linder and Hoskins¹¹ gave schizophrenic patients glycerin extract of the adrenal cortex by mouth in periods of five to thirteen weeks and in doses of 30 grains (2 gm.) to 450 grains (30 gm.) daily and obtained an elevation of the systolic blood pressure of 22 to 34 mm. the pulse rate and cholesterol level were significantly lowered. They concluded that such extracts were potent by mouth.

DeCourcy and his coworkers⁷ made use of subtotal bilateral supra-renalectomy for hypersuprarenalism and were able to reduce the blood pressure and in some cases relieve all symptoms of hypertension.

Hyperinsulinism—Harris¹² describes this condition as the hunger disease associated with weakness, nervousness, and other manifestations of hypoglycemia. It is the antithesis of diabetes. It has been recorded in children of diabetic mothers and is associated with hypertrophy of the islands of Langerhans. In mild cases the blood sugar ranges between 0.70 and 0.60 with a low sugar tolerance curve. More severe cases may have attacks of petit mal or grand mal. In the writer's experience, however, low fasting blood sugar in untreated epileptic patients is very uncommon. In the severe type of hyperinsulinism, the blood sugar is below 0.50 and readings as low as 0.27 have been found.

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American Academy of Pediatrics

Proceedings

ANNUAL MEETING OF THE EXECUTIVE BOARD

THE meeting of the Executive Board of the American Academy of Pediatrics was held at the Georgian Hotel, Evanston Ill., Dec. 1 1934. President Thomas B. Cooley presided, and all the members of the Board were present.

After a thorough discussion of the budget for the year, July 1 1935, to July 1 1936 it was decided that it would not be necessary to increase the initiation fee and dues for that period. The list of delinquent members was then taken up and definite action taken.

Question of the next annual meeting was discussed. It was decided that the plans could not be changed now; the meeting will be held at the Waldorf Astoria Hotel New York City June 7 and 8 1936. It was decided to hold four Panel Discussions, one set of Round Table Discussions, and one business meeting. The Panel Discussions are to last one and one-half hours each, and there are to be two to a session with a fifteen minute interval between. It was projected to have fifteen Round Table Discussions with a limit of thirty to each group. The contract with the George W. Hale Decorators, Inc. Buffalo N. Y. for the exhibits, was approved.

As to the future policy with regard to the annual meeting it was felt that that could best be taken up at the meeting where it could be discussed.

Dr. Cooley reported on his trip to Montreal to meet with Canadian physicians and the progress made in that section.

Region I—After discussing applications for fellowships, action on which will be reported in another issue, Dr. Schroeder reported that the next regional meeting would be held in the fall of 1935 in Philadelphia. Dr. Schroeder asked that an outline as to the duties of state chairmen be made. He was informed that a committee in Region III had already proposed to make such an outline and also that the Children's Bureau would be asked to cooperate.

Region II—Dr. Mitchell asked that he be allowed to call a meeting of the state chairmen of his region in the not distant future to discuss plans. The motion was made and carried that Dr. Mitchell be allowed to call such a meeting; expenses over and above the allowances of the states and region to be covered by the Academy.

Region III—Dr. Helmholtz presented the names of applicants and likewise announced that the next meeting of Region III would be held in St. Louis instead of Cincinnati, so that Regions II and III could hold a joint meeting about the time of that of the Southern Medical Association.

The following additions and changes in the Constitution and By Laws were recommended:

Article III. Change title to "Powers and Duties of Executive Board, Regional Committees, and State and District Chairmen."

Add Section 4 State, District or Provincial Chairmen The President shall, on recommendation of the respective regional chairmen, appoint a chairman for each state, district or province, as the case may be, in which the Academy is represented by Fellows

Section 5 The duties of each state, district or provincial chairman shall be as follows

(a) To keep himself informed as to the purposes and policies of the Academy and as to conditions in his district relating to these policies

(b) To promote association and cooperation between the Fellows in his district, to consider with them the problems arising there, and to assist and initiate when necessary activities in furtherance of the Academy's aims and purposes

Article III, Section 2, shall be changed to read from "at least five members" to "three members"

Dr Langley Porter, of San Francisco, and Dr Frank H Lamb, of Los Angeles, were elected Emeritus Fellows

Journal of Pediatrics—The motion was made and carried that the request of the Editorial Board, that Dr Irvine McQuarrie and Dr Grover F Powers be added to that Board, be granted Also, that the Executive Board was entirely in sympathy with the situation regarding the publication of the Round Table Discussions and that everything possible would be done to curtail the amount of material in these discussions They agreed that articles read at regional meetings should be submitted to the editors for their action as to publication

At the request of the Committee on Child Health Relations, Dr M Hines Roberts, of Atlanta, Ga, and Dr George M Lyon, of Huntington, W Va, were added to that Committee The Executive Board approved the following resolution proposed by this Committee

"That, wherever feasible, the state Academy groups undertake to inform themselves as to

(1) the status of child health activities carried on in their respective states by official and nonofficial agencies,

(2) the provisions for medical care and health supervision of children in institutions or under the care of child placing agencies and of children in their own homes whose families are unable to pay for medical service,

(3) the medical and health needs of special groups of children scattered throughout the state or concentrated in certain areas or communities, and

(4) the basic facts of mortality and morbidity among children in the state and its political subdivisions, for the purpose of appraising the work done and of bringing about improvement in the health supervision and medical care of children through the cooperation of official departments of health and welfare, medical societies, non official welfare agencies, and lay organizations

"The Committee on Child Health Relations would be glad to attempt the preparation of a brief outline giving suggestions for such an appraisal of child health activities if state groups desire it. The committee appreciates that certain state groups are already engaged in appraising and developing child health activities and does not intend to suggest any duplication of effort"

The Executive Board also approved the appropriation of sufficient moneys to meet the traveling expense for a meeting of this committee sometime in the near future, time and place to be determined by the chairman

Dr Grulee reported that, after a conference with Dr LeRoy Wilkes in New York, he felt sure that the Committee on School Health and School Health Education would have a definite report in the near future

It was voted that the Committee on Clinical Investigation and Scientific Research should be granted up to the amount of three hundred dollars to cover expenses between now and the first of June in an investigation to be carried on by that committee.

The Committee on Hospitals and Dispensaries reported that it was in the process of publishing the report on general hospitals and that it would next take up the report on communicable disease hospitals.

It was decided to change the name of the Committee on Relation to the Section of Diseases of Children of the American Medical Association to the Committee on Cooperation with Medical Groups and Societies. It was also decided to appoint a new committee the Committee on Cooperation with Nonmedical Groups and Societies. The Committee on Cooperation with Medical Groups and Societies was asked for recommendations for a permanent committee for the International Pediatric Congress, which is to be held in Rome in the summer of 1936. The Committee on Cooperation with Nonmedical Groups and Societies, when appointed, will be asked to take up the question of attendance of members of this Society at the meeting of the National Association for Nursery Education.

NEW BUSINESS

It was moved and carried that in the future a check for initiation fee must accompany each application for fellowship.

It was moved and carried that it be recommended to the Academy that after July 1 1937, no candidate shall be acceptable for fellowship in the Academy who has not been licensed by the Board of Pediatrics.

The question of an auxiliary membership for physicians interested in pediatrics was discussed, but no action was taken.

It was approved and carried that a floating fund for the use of those states whose membership does not bring sufficient revenue to carry on their activities should be established and should be available on application to the Secretary by the State Chairman.

Dr. Helmholz reported on the meeting of the National Society for Research in Child Development, the pediatric section of which he was chairman and Dr. Grulee was secretary. There is every reason to believe that the pediatricist will receive due recognition in this group.

Dr. Grulee reported upon the meetings in Washington of the Committee on Economic Security Child Health Section.

FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

Round Table Discussion on Prematurity

Cleveland, June 11, 1934

Leader Julius H Hess, Chicago Assistants Dr Ethel C Dunham, New Haven, Conn, Dr Warren R Sisson and Dr Stewart H Clifford, Boston, and Dr Edward A Wagner, Cincinnati, Ohio

The Round Table Discussion on Prematurity was called to order at 9 40 A M by Dr Julius H Hess, chairman

CHAIRMAN HESS—The care of the premature infant and his future development covers practically the whole field of pediatrics There are so many phases to it, many of which cannot possibly be covered in the time at our disposal, that I believe we will make this meeting more valuable by concentrating on a few subjects pertaining to the care of premature infants

I shall briefly review the work of our station with as little statistical reference as possible in order to open the field for general discussion.

The station at the Sarah Morris Hospital, which was opened in 1922 on a very small scale in one room, now has three large rooms and one small pumping station The following figures emphasize the demand for such a station in a large city, in fact, in any city In 1922 we received 19 cases, in 1923, 28 cases, in 1924, 47, in 1925, 66, in 1926, 106, in 1927, 138, in 1928, 167, in 1929, 190, and in 1930, 198, in 1931, 207, in 1932, 249, and in 1933, 208

I wish to call attention to the decreasing mortality rate beginning with 1928 This is largely accounted for by more complete cooperation of the obstetricians and our sending for the infants to avoid refrigeration. We had a total of 1,623 cases, prematurely born infants, and of these 1,135 lived and 489 died The mortality rate for all admissions is approximately 30 per cent, with our graduates numbering 70 per cent. Furthermore, we took in quite a number of full term immature infants Approximately 90 per cent of all admissions were charity cases, representing in considerable part the lower level of society in a large city The annual increase in the number of infants cared for offers the best evidence for the demand for similar stations

What we have tried to demonstrate is that these babies can be taken care of and that you can have a fair degree of success in the rearing of them with a minimum of equipment.

Our rooms are equipped with electrically heated, water jacketed beds, DeLee heated tables, scales, small wet and dry bulb hygrometers, and thermometers registering high and low room temperatures We also have a time clock, which we think is very essential, because we know when the nurse has registered the individual feeding time of the infant on the clock she must be awake, and as a consequence we know she probably feeds the baby

We believe our greatest success is due to the fact that we have a nursing corps that, up until recently at least, has changed very little Our head nurse has working

with her two other graduate nurses on eight hour shifts. We have a number of nurses for infants who have been there for a considerable period of time. Furthermore we have nurses in training. Up to about six months ago we required the nurses in training who received the service to apply for it, as a good many nurses are not especially interested in premature infants, and it would have been as much of a hardship on them to take this work as it would be on the babies to have them take it.

We are convinced that breast milk is the all saving infant food for premature infants. We start all our babies on straight breast milk. We usually have two or three sometimes as many as four wet nurses. Most infants by the third week depending upon their size have added to the breast milk a certain amount of skimmed lactic acid milk. We use either cultured lactic acid milk or powdered lactic acid milk. We add the lactic acid milk to increase the protein content of the mixture.

We had 1,623 premature infants, of whom approximately 70 per cent graduated. There were 1,423 who survived the first twenty four hours, 1,385 forty-eight hours and 1,378 ninety-six hours with 1,135 graduating. Of those who survived the first forty eight hours, 81.9 per cent were graduated.

I wish to emphasize the seriousness of refrigeration. We had 206 babies between the years 1922 and 1926 of whom 140 were born in the home, 53.5 per cent of those dying. We had 126 born in hospitals and only 42 per cent died.

Up to that time we did not send for the babies. Then we started sending for the babies, and there was a considerably lowered mortality for 1927 to 1930. During that period, we had 237 born in the home, with 40.5 per cent mortality and 259 born in hospitals with 25.1 per cent mortality.

TABLE I
DATA ON VITALITY OF PREMATURE INFANTS GRADUATED

BIRTH WEIGHT IN GRAMS	TOTAL ADMIS- SIONS	NUMBER SURVIV- ING FIRST 24 HOURS	NUMBER SURVIV- ING FIRST 48 HOURS	NUMBER SURVIV- ING FIRST 96 HOURS	GRADUATED		PERCENT AGE GRADUAT- ED OF INFANTS SURVIV- ING FIRST 48 HOURS
					NO.	PER- CENT- AGE	
Less than 1,000	77	34	26	23	12	15.5	46.1
From 1,000 to 1,500	316	213	200	198	187	43.3	68.5
From 1,500 to 2,000	606	559	562	550	456	75.2	82.6
From 2,000 to 2,500	500	496	492	492	486	87.2	88.6
From 2,500 to 3,000	69	69	69	69	61	88.4	88.4
Over 3,000	5	5	5	5	3	60.0	60.0
Unknown	50	47	41	41	80	60.0	73.1
Totals	1,623	1,423	1,385	1,378	1,135	69.6	81.9

From 1930 to 1934 we had 510 infants born in the homes with a mortality lowered to 24.5 per cent and 352 born in the hospitals with the mortality lowered to 22.5 per cent. Fully 90 per cent of this group were brought in by our own people in a little electrically heated ambulance. Of a total of 882 infants born at home, 272, or 71.2 per cent, were admitted to the hospital within the first twenty four hours during 1930-1932. Of a total of 372 infants born in the hospital, 207, or 76.1 per cent, were admitted to the station within the first twenty four hours during 1930-1932.

In our first 1,427 admissions, we had a known history of syphilis either by Wassermann test of the mother, father, or both, or a later Wassermann test of the child (118 cases with thirty two deaths). Toxemia of pregnancy was one of the most important conditions, with 131 cases of toxemia and thirty three deaths. Five were complicated by syphilis. Placenta previa totaled twelve. Multiple pregnancy, as might be expected, gave us the greatest number of cases, 322.

Observations at autopsies on 386 cases (488 deaths) included intracranial hemorrhage, 168, syphilis, 23, otitis media, 38, mastoiditis, 10, pneumonia, 70, enteritis, 27.

It is quite apparent that nature has been very kind to the infants with severe intracranial hemorrhage. Eighty six died on the first day, and 64, between the second and seventh days. One hundred one of these infants weighed less than 1,500 gm.

During the past six years, otitis, mastoiditis, and enteritis have been exceptional findings at autopsy.

We all want to know what happens to the infants after we get through with them. We have records of a total of ninety two cases of infants who died after discharge or after graduation. The greatest number of deaths are recorded as pneumonias or other conditions complicated by pneumonia. There were eighteen with uncomplicated pneumonia, three with empyema, six with otitis with pneumonia.

Among 1,134 infants who were graduated, 128 were considered as having had intracranial hemorrhage. Sixty nine of these had been under close observation during the past four years and have had from one to four physical and psychometric examinations. Of these, forty two show no demonstrable physical evidence of injury to the central nervous system. Eleven show evidence of severe physical injury with mental retardation in seven, and four show average intelligence. Seven show evidence of moderate physical injury, with mental retardation in four, and three show average intelligence. Nine show evidence of slight physical injury, with mental retardation in two, six show average intelligence, and one is classified as superior.

This study was carried on for the Institute of Juvenile Research, by Dr. George Mohr, and Phyllis Bartelme, Ph.D.

We were much interested in this particular phase of the subject because we wanted to know whether the work we had undertaken was really worth while. In other words, were we rearing a lot of infants who would not make good citizens? Were they actually worth the time and energy expended in trying to save them?

The number of spinal punctures has been reduced by fully 90 per cent in recent years. We formerly thought that spinal puncture was a valuable therapeutic measure in the premature infant. It is not of much value in most cases, especially if there is a very marked hemorrhage.

Saphir and Levinson made a study of intracranial hemorrhages, and they believe the minimum amount of damage was due to the fact that there is a minimum tendency toward organization of the clot. If there is much hemorrhage or severe injury, the infants die.

Emergency Therapeutic Measures—Oxygen therapy. All infants weighing under 1,200 gm, those showing respiratory and cardiac embarrassment, and all others who, it is believed, might be benefited by oxygen therapy are placed in an oxygen chamber.

During the three years 1931 to 1934, 346 of the 792 infants admitted have been placed in the oxygen chamber. Most of them have been kept there for more than twenty four hours, and in a few cases for as long as six weeks or more. With a few exceptions the infants were kept in a 40 per cent oxygen atmosphere.

Intraperitoneal administration of fluids, as an emergency measure, is to be avoided because of the dangers of intestinal perforation and interference with the cardiac and respiratory functions. Blood is the only thing we put in the peritoneal cavity, and that not often.

DR. W R Sisson (Boston, Mass.)—My only reason for being here is to introduce Dr Clifford and to tell you about the background of the work we started and which Dr Clifford has organized.

The study of this material which consists of some 900 premature infants really dates back about ten years. It is of the utmost importance that the premature service should be extremely well organized and that one man, if possible, should be constantly in attendance. We have developed at the Boston Lying In Hospital a premature service of which Dr Clifford is head and which is manned by internes from the Children's Hospital. A close medical relationship between the obstetric and pediatric services has evolved which has been the fundamental reason for making this work possible.

Better housing has been accomplished in air conditioned rooms where the humidity and the temperature can be controlled at the most favorable points. I believe the humidity and the temperature alone have not been as important factors as the new building, the new organization, better nursing, and all that has gone with it. A great contribution from the study is the knowledge that premature infants have an optimum physiologic efficiency at a lower body temperature than we formerly believed. They now are kept at temperatures of 97 to 98 F, and progress at this lower temperature perhaps a little better than when their temperatures were kept at a level of 99 to 100 F.

Dr Clifford has been studying the relationship of prematurity to the general obstetric problem and has created interest in reducing the number of premature births.

The problem of feeding these babies interests me especially. Babies who will not nurse are gavage as a routine after the second day. As long as they show signs of physiologic prematurity, that is, when their nursing instinct has not developed, and other stigmas of prematurity are obvious, most of the babies are fed at four hour intervals.

The problem of infection in the care of premature infants is almost a thing of the past in a well organized clinic.

We have not made a careful study of the babies after they have left the hospital.

We will never get anywhere in the comparison of statistics in the various clinics until we understand what a premature baby is, what a stillborn is, and various other very fundamental terms and methods in order to use the same language.

CHAIRMAN HESS.—Dr Sisson, have you a permanent nursing force or are you using all of your nurses that are in course of training?

DR. Sisson.—For the past few years our clinic has been run by a full time nurse whom we have trained, and now she is as capable as any physician in carrying out all the work of the premature nursery.

We also have nurses transfers from other hospitals, who are affiliating with the Boston Lying In Hospital. I spend a definite number of months in the general clinic. With the exception of the supervisor the premature nursery staff changes every few weeks. The routine gavage feedings have been given by the student

nurses, after instructions by the supervisor, without ill effects. We should have probably two graduate nurses because sometimes night supervisors are not as efficient as day supervisors. It is absolutely essential that some experienced person should be in the nursery all the time.

CHAIRMAN HESS—The reason for that question is that the nursing situation has bothered us very materially, especially as it concerns gavage feeding, since we have more nurses who are in training for shorter periods of time.

DR. O. L. STRINGFIELD (STAMFORD, CONN.)—What size tube do you use?

CHAIRMAN HESS—We use a No. 12 French catheter. Each baby has an individual catheter, which is marked at three different places with indelible ink. The first mark is the distance from the tip of the ensiform cartilage to the bridge of the nose. The second one is 2 cm. above that, and the third one 2 cm. above that. When the catheter is passed to the first mark, the tip is from 1 to 2 cm. above the cardia. Most of our feedings are done with the catheter at that point without entering the stomach.

The catheter is always passed with the funnel empty. The barrel of an ordinary glass syringe is used as a funnel. If there is marked distention of the stomach, which is recognized if the wall of the abdomen shows the outline of the stomach, the catheter is passed to the second mark. Sometimes it is necessary to pass it to the third mark to empty the stomach of air. The average feeding time is about three minutes. The catheter must be compressed while it is being withdrawn.

Most of the feedings other than those given by gavage are given with a medicine dropper with a little piece of rubber tubing over the end of the dropper.

DR. ETHEL C. DUNHAM (NEW HAVEN, CONN.)—We very rarely use catheter feeding in our clinic because we have considered it dangerous. In view of the mortality rates reported by Dr. Hess, as well as those reported by Dr. Sisson and Dr. Clifford, one will have to admit that it certainly looks as if catheter feeding, as carried out by them, is probably not very dangerous.

Not long ago I visited a hospital where nearly every premature infant was fed by catheter. The impression of those in charge was that the mortality rate was high, but they had no figures to support this belief. The pathologist at this hospital, however, stated that the incidence of aspiration pneumonia was high. I feel that catheter feeding is not an innocuous procedure. It is only when we compile figures and analyze cases that we have a right to say whether it is a good method of feeding or not.

CHAIRMAN HESS—It is also true that the worst cases, the smallest and the weakest infants, are the ones fed by catheter. We are feeding by catheter those who have not pharyngeal reflex enough to swallow.

DR. EARL W. MAY (DETROIT)—Out of 206 premature infants last year, there were three who we thought at autopsy might possibly have had trouble from catheter feeding. We fed by gavage all those infants who showed difficulties in swallowing during a test feeding with the dropper or Breck feeder.

We have a group of six graduate nurses, who are trained in catheter feeding, for the twenty-four hours so that we can rely on gavage at any time.

CHAIRMAN HESS—We have a clinic for graduates, and we can account for about 550 of our graduates of the last fourteen years.

Our social service nurse follows them into the home, and when they are old enough, weather permitting they are brought into the clinic and followed very closely. We used to see much rickets and tetany. They have practically disappeared from our picture. In the case of syphilitic infants our good results have been due to the fact that we have been able to follow them very closely. Within twenty-four hours a nurse is in the home to see that the mother keeps up her breast milk supply. Many of these babies, after three, four or eight weeks, go home to their mothers' breasts. In the meantime, it is a very profitable thing, because one half of the breast milk used in the station is furnished by the mothers of these babies. The breast milk supply is for the mother's baby and is usually enough for two or three more babies during the greater part of the time the baby is in the station.

DR STEWART CLIFFORD (BOSTON) —I would like to clarify one or two points so we can all be talking about the same thing. Dr Hess's premature station and Dr Blackfan's at the Children's Hospital are not run in connection with a maternity hospital. In talking over our problems at the Boston Lying In Hospital with Dr Blackfan, we have found that what seems advisable for the babies under Dr Blackfan's care and probably the babies in Dr Hess's Clinic may not seem necessary or even advisable for the babies in the maternity institution's premature nursery. The explanation lies in the fact that different types of patients are encountered in the two institutions.

Our babies are transferred to the nursery within a very few minutes of birth, without the factor of exposure and infection being introduced. The group that is treated at the Children's Hospital, and possibly in Dr Hess's group, may be received after an attempt has been made in an outlying home or hospital to make the best of a premature baby situation. Then in a panic a baby will be rushed in, possibly in extremis, terribly dehydrated, and in very poor condition. Even if brought in immediately he is exposed to outside infection and possible chilling. Before we can compare methods of treatment and mortality statistics we must be sure we are considering like cases from comparable institutions. The mortality statistics from maternity hospital nurseries should be lower than from a non-maternity institution. If this proves to be true, we should organize obstetric hospitals so they can take care of their own premature babies without the exposure factor and the infection factor leaving the premature station in the children's hospital to care for those born in stations not properly equipped and the infants born in homes inadequate to meet their needs. The general situation in Boston would certainly be far more grave if it were not for the premature station at the Children's Hospital.

It is essential also that we have some common definition of terms. The reports from various clinics should be comparable and prevent the "whitewashing" of statistics. "Let's have no miracles between friends" is apropos of the premature infant situation, when a hospital can report a premature infant mortality of 10 or 15 per cent. Looking at the figures reported for comparable institutions in different parts of the country, I was struck by the fact that while the premature infant mortality rate a number of years back started at various figures from 60 to 80 per cent, and has been lowered through the combined efforts of methods such as Dr Hess has outlined, the plateau seems to be somewhere around 30 per cent, a fixed point below which present methods cannot go.

We have defined as premature, any baby weighing five pounds or less. We also include as a premature infant any baby whose heart is beating at birth, even though

he doesn't breathe and may only take a gasp. In other words, we are trying to get an uncorrected picture of the premature infant situation that will give us a point of attack for future study.

Using this classification, in the past eleven years the premature infant mortality rate was reduced from around 50 to 60 per cent to a level somewhere around 30 per cent. For the past six years, up until last year, our premature infant mortality, the gross, uncorrected mortality, was around 30 to 35 per cent. Nothing we could do, including an air conditioned premature nursery, which you have heard described, in any way depressed the premature infant mortality beyond that point. We thought when we introduced this expensive air conditioned equipment, we should see an immediate drop in the premature infant mortality. The mortality for the next year, as a matter of fact, was a little higher than it was the year before.

The premature infants, comprising only 3 per cent of the total deliveries, were responsible for over half of the deaths that took place during the lying in hospital period. This included only the premature infants that were born alive. The premature infants also compose a large per cent of the stillbirths.

We have been attempting a new approach to a further reduction in this residual mortality. A statistical survey was made of the records of our 900 premature infants showing that over 85 per cent of all the deaths took place in the first forty eight hours of life. It seems perfectly reasonable that if the premature infants die in the first forty eight hours of life, no air conditioned nursery, no system of catheter feeding, no system of nursing care, no system of prevention of infection, no pediatric methods could be of any avail in reducing the mortality. This makes a reduction of the mortality of the first forty eight hours an obstetric problem.

We found there is a very striking decrease in the premature infant mortality with each 8-ounce increment in body weight. Therefore, if we could increase the body weight merely 8 ounces, we would thereby get a better group of premature infants and, obviously, lower the gross mortality.

We also discovered that the infant during the fifth lunar month gains about 4 to 5 ounces, in the seventh lunar month around 6 to 8 ounces, and in the ninth lunar month anywhere from 10 to 12 ounces a week in utero. One or two weeks' delay in the induction of labor will often amount to an increase in the weight of the fetus from 1 to 1½ pounds. It is quite apparent, therefore, that even a two week delay will improve the outlook for the premature infant at birth.

The work of Scammon and Caulkins has demonstrated that the occipitofrontal diameter is an accurate index of the age of the fetus. This gave us the idea that if the occipitofrontal diameter of the fetal head could be measured by any method in utero, we would immediately at any period of pregnancy be able to ascertain the fetal age of the infant in utero. A method was investigated and finally, after several years of work, perfected so that by roentgenometric technic we are now able to measure accurately the occipitofrontal diameter of the fetal head in utero. As at the present time we are unaccustomed to thinking in terms of the occipitofrontal diameter, it was necessary to translate that to the term of body weight.

The relation between the occipitofrontal diameter and the birth weight was investigated in over 600 newborn infants, and a graph, which you might be interested in seeing, was prepared so that from any occipitofrontal diameter measurement we can predict the probable maximum and minimum weight of the fetus in utero.

With this accurate knowledge of the body weight in utero, many pregnancies can be prolonged until a more viable baby is assured. On the other hand, in the case of certain complications of pregnancy, when the obstetrician has been leaning

over backward in an attempt to get a viable baby he will find that the baby is already of sufficient size that there is no necessity to expose the baby further to the danger of fetal death in utero or the mother to the hazards of a further prolongation of pregnancy and that pregnancy may immediately be terminated.

We found that 28 per cent of premature babies who were born alive were born of toxemic mothers. We found that, roughly 12 per cent of the toxemic group delivered stillborn babies, half being premature, who, if delivered the week before might have had a good chance of living. Therefore, in toxemia, the fetus was found to be exposed to a double hazard (1) if delivered too early, it would die of prematurity, (2) if delivered too late the placenta would become grossly infarcted or prematurely separate and the baby would be stillborn.

In investigating fifty five cases of toxemia we have found that the level of the mother's blood pressure may be an index of the probability of the production of a stillborn infant. In levels up to 150, we very rarely encountered a stillborn infant. In the level of blood pressure from 150 to 180 11 per cent of the toxemic mothers had stillborn infants. When the blood pressure reached 180 or 210 43 per cent of all the toxemic pregnancies resulted in stillborn infants.

Therefore, if a mother's blood pressure is 200, and the fetal size in utero is from $3\frac{1}{2}$ to 4 pounds continuing pregnancy and gambling for a larger baby exposes that baby to 43 per cent hazard of being stillborn. We know statistically that if delivered at once the baby at this weight will face about a 20 per cent mortality. Under these circumstances the future of the fetus is much brighter as a premature baby than to be carried on to term with greater chance of being born dead.

It is thus seen that what actually began as a method of reducing the number of premature infants has ended as a method whereby we are actually increasing the number of premature babies, but we are decreasing the number of stillborn babies. Over a ten year period, the stillbirth rate was at a very high level, but last year for the first time there was a drop of almost 20 per cent in the stillbirth rate. Those babies that were salvaged were the premature babies that if allowed to continue to term may have been born dead. Conversely the incidence of prematurity, that has been going along at a very uniform rate of around 27 per 1,000, increased last year to 34 per 1,000 and the increase, we believe, was largely in the babies that were salvaged from the stillborn group.

A further study was made of the different methods of delivery and their effect upon the viability of the premature infant. We found to our amazement that what was thought to be the safest method for delivering a premature baby cesarean section, was actually the most dangerous. Fifty per cent of the cesarean deliveries of comparable weight groups resulted in dead fetuses and the safest possible method for the delivery of the premature baby was the normal delivery with vertex presentation with low forceps and wide episiotomy. The figures are quite striking for the two different methods of delivery.

Apparently toxemia exerted no direct influence on the premature infant mortality rate. Toxemia, on the other hand did affect the fetus indirectly. Through involving the placenta, the fetus is poorly nourished and approaches the minimum weight to be expected from its skeletal measurement. If the pregnancy is not terminated in time, toxemia may result in the death of the fetus through the mechanism of placental involvement that has been mentioned.

We found that in cases with heart disease, when heart disease was accompanied by failure and signs of decompensation the premature infant mortality was 80 per cent. The reason advanced for this high rate is threefold (1) these patients

had to be delivered by cesarean section, (2) 73 per cent of them received morphine prior to delivery, (3) the placenta and, indirectly, the fetus shared in the failing circulation and was thus unfavorably influenced

Therefore, in handling a patient with heart disease when there is an 80 per cent mortality for the premature infant when failure develops, it is far better to gamble on the 3 or 4 pound baby a week or so before the mother may possibly break than to gamble for a larger baby and have failure set in.

In this very rapid survey we find that we have been unable by ordinary pediatric methods to bring the gross premature infant mortality below a fixed level, that most of the mortality we have been unable to influence has been that which occurred during the first forty eight hours of life and therefore was principally an obstetric problem, that there is some prospect of influencing this mortality the first forty eight hours, and therefore the mortality rate of the premature infant as a whole, through a study of the factors influencing the fetus in utero and determining, if possible, the safest method of delivery, the optimum time for delivery, and so forth. There is opened a whole new pediatric field in which we are extending our frontier to include the fetus in utero. The surface has just been touched, many of the opinions that we at present hold will have to be revised as our experience grows, but the results of the past year are very suggestive that we may be on the right track for really effecting a considerable reduction in the premature infant gross mortality rate.

DR EARL W MAY (DETROIT) —We can definitely lower the mortality rate when we handle the babies right from the time of birth, and we have lowered it below 30 per cent. The question of how many hours should be eliminated, twelve hours or twenty four hours, should be brought up and definitely decided.

We do not feed breast milk at all to the babies of toxemic mothers, tuberculous mothers, mothers with heart complications, and such types. They are fed a formula because the babies, within a short time, will have to be accustomed to a formula. There has been no greater death rate among the formula fed babies than there has been among the breast fed babies. When we know that a baby of a toxic mother will eventually get on to the breast, it is fed on fortified breast milk, with 2 to 3 per cent of carbohydrate in the form of dextrimaltose, dextrin, etc., added.

CHAIRMAN HESS —Dr Dunham, in quoting your statistics, would you like to bring out that question of what time period we should eliminate in our statistics? I might say that in our charts we have divided them into four groups as follows: all infants received, those that live twenty four, forty eight, and ninety six hours.

DR. CLIFFORD —The technical description of the method appeared in *Surgery, Gynecology and Obstetrics* in April (Vol 58, pp 727-736, 1934). The chart you saw and the application of the method to the determination of the fetal size appeared in *Surgery, Gynecology and Obstetrics* (Vol 58, pp 959-961, 1934). A preliminary discussion of the obstetric management of premature labors appeared in the *New England Journal of Medicine* (Vol 210, pp 570-575, 1934).

CHAIRMAN HESS —I am going to ask Dr Wagner to discuss intracranial hemorrhage.

DR EDWARD A WAGNER (CINCINNATI, OHIO) —I shall describe our experience at the Cincinnati General Hospital.

Statistics show that about two thirds of the newborn infants coming to autopsy show some evidence of intracranial hemorrhage. In sixty two necropsies on pre-

mature infants at the Cincinnati General Hospital, there were thirty-one instances of intracranial hemorrhage and twenty-five cases of ntelectasia.

As the greatest factor in premature mortality, this condition deserves our deepest interest, not only as a cause of mortality but also as related to physical and mental handicap. Although some observers are attempting to minimize the importance of intracranial hemorrhage as the great cause for mental retardation and spasticity, stating that congenital brain defects and encephalitis have been overlooked as causative factors, experience leads us to believe that intracranial hemorrhage is still by far the most common cause.

The newborn are particularly liable to bleed, and premature infants are even more susceptible to hemorrhagic occurrences because of several factors. The brain capillaries are new endothelial tubes without elastic or muscle fiber. Anesthetic drugs may lengthen the bleeding time. Hemolysis of the red cells occurs from the time of birth when the baby is exposed to atmospheric conditions of oxygen tension. Bile salts accumulating are also a factor. Deficient protein intake of the mother during pregnancy is a factor. Hemorrhagic disease as an entity is also a factor. Syphilis and sepsis come as later factors.

Variations in intracranial tension during labor and on expulsion undoubtedly play a rôle. Molding of the head is unquestionably a cause in some instances, as is the sudden springing back of overlapping bones.

Hemorrhages as you know occur over the cerebrum, in the cerebellum in the brain substance, into the ventricles, and sometimes in the medulla as shown by Hemmuth and Canavan. Their interesting observations showed microscopic hemorrhage in the medulla oblongata in 64 per cent of a series of autopsies. In twelve cases an anatomic diagnosis was established which would otherwise have been listed as asphyxia, swallowing of amniotic fluid, or possibly faulty feeding by gavage.

The Roberts method of injecting postmortem mercury or iodized oil into the circulation (the body being x-rayed) after the injection, is excellent for studying the location and extent of hemorrhage. Allen McClure has also elaborated this technique, injecting a substance called roentgen in the carotid.

Symptoms.—In the full term baby apathy, failure to nurse, irritability, and so forth, aid us in making a diagnosis. In the premature these signs are of comparatively little value for obvious reasons. Fretfulness, failure to gain in weight, and early fever are possibly of some importance. Cyanosis occurring intermittently is of distinct value as a diagnostic symptom. Those infants with continuous cyanosis frequently have congenital heart disease or ntelectasia. Muscular twitchings occur about the eyes and face in about 58 per cent of the cases.

Stern and Schwartz emphasize particularly nystagmus occurring during the first few hours of life.

Convulsions, localized or generalized, suggest the possibility of this condition. Hypertonicity is frequently associated with intracranial hemorrhage and may be so marked that when we attempt to elicit the Chvostek sign, general convulsions result. Reliance on flaccidity is of even greater importance than spasticity. Focal signs are of comparatively little value, and in many cases little dependence can be placed on them for localization.

Signs of intracranial pressure, such as bulging of the fontanel, are of importance. However in subtentorial hemorrhage a rather flat fontanel or a depressed fontanel may be found.

The eyegrounds are of comparatively little aid in diagnosis. Spinal puncture reveals increased pressure as a rule up to as high as 50 mm. Examination of the

spinal fluid frequently reveals blood, the finding of crenated blood cells being of the greatest importance. Xanthochromic fluid could be found in other conditions, but frequently occurs in intracranial hemorrhage.

Cisternal puncture is of distinct value as a diagnostic measure, whereas the lateral ventricle puncture is a rather dangerous procedure.

We have particular difficulty in differentiating intracranial hemorrhage from edema and hemorrhage occurring in hemorrhagic disease and hemorrhage occurring in skull fractures.

Most of the prophylaxis of this condition is unquestionably in the hands of the obstetrician.

As soon as the infant is born, we should avoid rough handling, particularly of methods used in resuscitation.

For the last seven years, I have advocated the use of intramuscular injection of human blood as a routine procedure in all premature infants. While it is well known that trauma with labor causes many hemorrhages, there is still a fair percentage of cases without evidence of trauma in which spontaneous bleeding occurs, either as a result of hemorrhagic disease with its lack of prothrombin or incompleteness in coagulating mechanism, or possible sepsis, syphilis, or other causes mentioned before.

In all cases of suspected hemorrhage, it is advisable to test bleeding and coagulation time, and in those cases in which there is a prolongation, repeated injections can be given. The subscapular region is far safer and less painful than the buttocks, and there is less tendency to infection and sloughing. Since instituting this procedure, we have had no instance of hemorrhagic disease in the last 400 cases.

The treatment of intracranial hemorrhage, other than the prophylactic treatment, resolves itself into the use of repeated spinal punctures or cisternal punctures. Other operative procedures, as a rule, are not to be recommended.

DR DUNHAM—I would like to ask Dr Wagner what the incidence of hemorrhagic disease was before he began to use these prophylactic injections of blood.

DR WAGNER—I can't give you the exact figures now.

DR DUNHAM—Among more than 900 infants in my series there were only three cases of hemorrhagic disease.

DR CLIFFORD—One in at least 800, and probably 1,000.

DR DUNHAM—So it would seem that the incidence is very low in a large series of cases.

CHAIRMAN HESS—What did you say the percentage of intracranial hemorrhage was to your total?

DR WAGNER—In sixty-two necropsies, there were thirty-one instances.

CHAIRMAN HESS—About 50 per cent—ours ran a little less than that. I mention that because of the fact that Dr Blackfan in his monograph reported only eight cases in a total of 163 deaths. Then, looking back in his statistics, I find that only forty-three of his 206 reported were two days of age or less when received. We receive 70 per cent of our infants in their first twenty-four hours of life, which might easily account for the fact that he has such a low percentage whereas you and I, in our clinics, have such a high percentage. Forty-eight and seven tenths of our deaths occurred in the first forty-eight hours after the infants were received at the station.

DR. DUNHAM --I want to discuss two subjects one, the question of mortality from prematurity, the other, the importance of having some graphic way of recording the progress of the infant from day to day

When the infant mortality rate for fifteen years (1917-1932) is shown in a curve, a satisfactory fall in the death rate under one year is seen. There is, however, only a slight tendency for the neonatal mortality to fall. The mortality under one day is represented by a nearly straight line practically no reduction of death rate in this age period having been made. Since at least 50 per cent of neonatal deaths are due to prematurity some reduction in the neonatal mortality rate would in all probability be brought about by improvement in methods for the care of premature infants

Two years ago I visited 105 hospitals in a large number of cities throughout the United States. All kinds of hospitals were seen, university clinics, general hospitals and children's and maternity hospitals. In each of these I asked those in charge what sort of results they had in the care of premature infants. In a majority of the hospitals visited, the answer whether favorable or unfavorable, was not based on figures. In fact there were only five or six hospitals in which figures were available at the time of my visit. At my request, however, figures have been compiled in a large number of these hospitals and sent to me for analysis

Before we can draw conclusions as to results of care, however, agreement must be reached with respect to criteria for the diagnosis of prematurity. I will not attempt a discussion of the different methods which have been advocated for determining prematurity because they are all thoroughly discussed in the literature. We must obviously agree on some basis for diagnosis which we can all use. Although for a number of reasons weight is not the most satisfactory criterion, nevertheless, we are almost obliged to use weight as the basis for diagnosis since it is the one measurement almost invariably made. Twenty five hundred grams or 5 pounds 8 ounces is the weight that is commonly used as the dividing line between maturity and prematurity

In the figures I have compiled, I have used 2,500 gm. or under as the basis for diagnosis of prematurity. Stillbirths were excluded. Every live-born premature infant whether it lived one second or longer, was included.

It is very important, when compiling figures on results of care of premature infants, to consider the infants in different weight groups, because the mortality will vary inversely with the weight of the infant that is, the smaller the infant the higher the mortality rate. I have used the following weight groups: less than 1,000 gm., 1,001 to 1,500, 1,501 to 2,000, 2,001 to 2,500

In the thirty-five hospitals from which I obtained figures there were 2,609 premature infants born, and of that number 957, or 37 per cent, died. The mortality varied between 92 per cent in the lowest weight group (less than 1,000 gm.) and 17 per cent in the highest weight group (2,001 to 2,500 gm.)

In one of these hospitals analysis of the data for a period of five years showed that the mortality among premature infants was increasing. This had not been previously realized and created much interest among the staff and brought about changes in their methods of treating premature infants.

In a series of 117 premature infants born in the New Haven Hospital the mortality was found to be 30 per cent, varying between 100 per cent in those weighing less than 1,000 gm. and 4.1 per cent in those weighing between 2,000 and 2,500 gm.

In a short time we hope to have some sort of a program drawn up so that with the cooperation of different hospitals and clinics studies similar to these may be made. A concerted effort to improve methods of caring for premature infants should result in a decrease in neonatal mortality

Some of us are not dealing with as large numbers of premature infants as Dr Hess and Dr Clifford in their clinics. Many of us have much smaller clinics or only a few premature infants to care for in private practice. In discussing the care of the premature infant with individual physicians, I sometimes feel that they are not getting a bird's eye view, so to speak, of the method of treatment they are using. We have developed a graphic chart which we find helpful, and I am going to try to point out to you the advantages of using some sort of chart even if caring for only one infant. (Chart shown.)

The chart shows graphically for each day of life, the temperature, weight, amount of vomiting, total number of stools, composition of the milk as to percentage of protein, fat, and carbohydrate, and caloric value per kilogram of body weight and total fluid intake. By the use of one of these charts one can see at a glance the point at which the infant begins to show signs such as fever, vomiting, etc., and the exact time relationship between the symptoms and the food and fluid intake on that day. In this way one can often see some slight deviation from the normal before it would be noticed if it was necessary, as with the ordinary case history, to turn over a lot of pages. I do not present this as an ideal chart, but only to point out that a graphic representation of the infant's course is helpful as a guide to treatment.

I wish to add one more point. Some authorities consider breast milk absolutely imperative in the feeding of premature infants, others state that gavage in the feeding of premature infants is life saving, some say that the temperature must be kept normal (98.6° F), whereas others say that this is not necessary. I do not think one has a right to make any statement unless one has some statistical knowledge of results of different types of treatment. In the New Haven Hospital clinic we use neither breast milk nor gavage as a rule, and I think the mortality rate compares favorably with other clinics where breast milk is used exclusively and gavage is used frequently.

No doubt many of you have very definite ideas about the treatment of premature infants. I hope that you will all compile figures, if you have not already done so, and give us the benefit of the methods used backed by figures on results.

DR CLIFFORD—May I just say a word about what seems to be a very minor point, but in reality, from the statistical point of view, is of very great importance, that is whether we take 5 pounds or 5½ pounds as the upper limit of the premature infant.

I can't give you the figures at 5½ pounds, but I can give you an illustration. We have a little more than 100 babies per year delivered in the hospital who weigh 5 pounds or less. We have about the same number who weigh between 5 and 6 pounds delivered per year. The babies who weigh from 5 to 6 pounds have a 3 per cent mortality, and the babies who weigh from 4 to 5 pounds have an 11 per cent mortality, and thus it increases as the weight decreases. We have had in the whole group of babies weighing from 1 to 5 pounds in the last year a 29 per cent mortality. If we include the babies up to 5½ pounds, we immediately introduce 50 babies with only two deaths, so that on this basis we could claim a premature infant mortality of 20 per cent.

If we are attempting to reduce the premature infant mortality, we will get a more dramatic picture of our results if we limit ourselves to the high mortality range of from 1 to 5 pounds rather than include the ones above 5 pounds who do fairly well anyway. If we want to produce statistical evidence of improvement in the situation, it is just as well to paint the picture as black as it is to begin with.

DR. DUNHAM—If twins are included in mortality statistics the mortality will be lower, because a twin weighing, for instance, 3 pounds may be mature and has therefore a better chance of survival than a premature infant of the same weight.

CHAIRMAN HESS.—The question of breast milk feeding is really a social problem. In the last year or two our charity cases have run up to about 80 per cent. We used to run about 70 per cent. Some of our babies come from the very poorest homes and if we can send those babies home on breast milk or have breast milk for them when they get home, it certainly means we are going to have not only a lowered mortality but a decidedly lower morbidity. That is one reason we have made such a strenuous effort to keep up all the breast milk in the homes we can. Also it is economy for us to receive the breast milk from the mothers while their infants are in the station.

What has been said about intracranial hemorrhage by Dr. Wagner and others is only too true. Many of them are not diagnosed as intracranial hemorrhage until they come to autopsy. Again we diagnose some intracranial hemorrhage which are not. I think the most valuable lessons we have learned have been from our post mortems. We have had 77 per cent of autopsies.

DR. EARL W. MAY (DETROIT).—We have been using adrenalin now for over a year and a half, and I believe it has lowered our premature infant mortality. We give 1 minim every hour to the very small babies, until they show definite signs of activity. That may be for three or four days, and then we give 3 minims every four hours. To some of our very weak premature infants we give that right along 3 minims every four hours until they are quite definitely active. Then we give it every eight hours, then every twelve hours, and twenty four hours, until it is discontinued. I feel that the adrenal glands are not overly active in these very small premature babies.

CHAIRMAN HESS.—We do not feed our infants during the first twelve hours and when they are in poor condition not for twenty four or even for thirty six hours. When they are left at home, there is always the danger that they will be given some form of artificial feeding.

In the four years 1927-1930 the total admissions of newborn and some days older premature infants and immature infants was 718. The deaths due to pneumonia in this group numbered thirty six.

In the three years 1931 to 1933, when the oxygen chamber was in use the total admissions of newborn and some days older premature infants and immature infants were 712. Thirty four of these infants had pneumonia, with eleven deaths.

In the three years 1931-1933, eighty infants who had graduated from the station were readmitted for various causes. Eleven of these infants died. Pneumonia was diagnosed in seventeen and was recorded as the cause of death in five instances.

Summary of Results Obtained With Oxygen Therapy.—Station mortality among 792 infants. Six hundred twenty eight, or 79.3 per cent, were graduated. Classified as unavoidable deaths were intracranial hemorrhage 62, congenital anomalies, 18, sclerema neonatorum, 2, syphilis, 4, athrepsia, 4—aged 13, 17, 51, and 57 days on admission, and lived 1 day, 5 days, 3 hours and 5 days, respectively, and also 44 infants with vitality so low that they did not survive the first forty-eight hours after admission to the station. This latter group included newborns and those several days old upon admission.

This leaves nineteen infants to be analyzed as to the desirability of classifying them as cases in which infections, both primary and secondary and other pathologic conditions might be directly related to their existence in the station.

Atelectasis 2 newborn infants—lived four and fifty eight days

Pneumonia 9 cases—7 in newborn infants who died in 6, 6, 9, 12, 23, 38 and 62 days, respectively. The associated pathologic conditions are given in detail elsewhere. Two were admitted at three and five days of age and lived 85 and 49 days.

Otitis media 2 patients admitted with otitis when 6 and 7 days old, and lived 19 and 7 days.

Pyemia 4 cases—two newborn, lived 25 and 16 days, one four days old on admission lived 4 days, this infant was in extreme condition when admitted, one admitted when 5 days old with omphalitis and with secondary pyemia.

Cerebral abscess 1 newborn infant who lived 12 days.

Thrombosis of the pulmonary vein with infarction of lung 1 newborn infant who lived 16 days.

Among these nineteen infants are two with atelectasis and two with pyemia (last two of whom were undoubtedly infected on admission), all four of which might well be considered as unavoidable deaths. The remaining fifteen are classified as station mortality and represent 19 per cent of all admissions during 1931-1933.

I had a chemist working for four and one half months on the study of our oxygen chamber. We tested the chamber using very small premature infants, larger premature infants, full term babies, and babies up to six months of age. We treated babies with pneumonia and babies with other types of infection, so that we covered the field of infants up to six months of age pretty carefully in our preliminary study before we introduced the oxygen chamber into our wards.

The chamber which we use is nothing more than the water jacketed, electrically heated bed which we have been using for the last eighteen years equipped with the new oxygen unit which fits on it as a lid. Ordinarily we use two liters per minute. Our oxygen costs us a little less than \$2.50 for a large tank. We use the commercial oxygen, and it costs us about \$1.25 per day to run our chamber.

In no case did we find a higher accumulation than approximately 1 per cent of carbon dioxide in the chamber, and that, of course, with the larger infants and with those who had a high temperature. Our greatest trouble has been with large babies with high temperature in keeping down the humidity. For that purpose, we use with the oxygen unit an ice chamber which is part of the equipment which comes with the oxygen unit. According to the size of the baby and the amount of fever which he has, it must be refilled with cracked ice every two or three hours. In the presence of a high temperature in a large infant (a six month old baby is about the largest you can put in these), we have to add some salt at times to our ice to accelerate melting.

The newer beds are also equipped with little faucets so that you can hook rubber tubing to your ordinary running water in the ward and cool the bed with running water instead of ice.

We believe we have resuscitated a fair percentage of babies who otherwise might not have lived, and we do believe our pneumonia statistics are very much better. It is a comparatively inexpensive way of administering oxygen.

DR C O TERRELL (FORT WORTH, TEXAS)—What was the time after birth you began feeding those children?

CHAIRMAN HESS—The earliest we feed any baby is the second twelve hours. During the second twelve hours in the average infant we start off with six feedings, four of water and two of breast milk, from 2 to as much as 15 c.c., the amount varying with the size of the baby and its reaction to the feeding. The second day we feed regularly, our babies are fed every two hours.

I want to emphasize a point Dr Dunham brought out in her chart, that we keep track of the total fluids. We think the amount of water the infants get should be as carefully noted on the chart as the amount of food they get.

I also want to emphasize the fact that if you want to run a station successfully you must have at least one person who knows the job and who is on it all the time. That is the secret of what success we may have had.

DR. DUNHAM.—May I ask if you would tell us why you use oxygen rather than a combination of CO_2 and O ?

CHAIRMAN HESS.—Miss Woodward who did my chemistry while testing the oxygen unit used the CO_2 oxygen in her work. We believe we can accomplish every thing claimed for CO_2 oxygen with oxygen alone. I personally haven't seen any advantage otherwise in the use of CO_2 .

DR. DUNHAM.—There are no doubt, indications for using oxygen alone or for using CO_2 and O combined. I think there is great lack of any evidence, however, as to what the indications are since studies of the infant's blood seem not to have been made.

CHAIRMAN HESS (Slide).—Here are four babies who were in our station at one time last summer, admission weight 865 gm. birth weight, 825 gm., admission weight, 700 gm. admission weight, 800 gm. These pictures were taken when they were fifty-four, twenty-four, one hundred twelve, and seventy-four days old. Three of these babies are alive and doing well today. The fourth contracted pneumonia several weeks after graduation and died in another hospital.

DR. TERRELL.—In these very small children, do you find it necessary to give peritoneal fluid to get the amount of fluid intake you desire?

CHAIRMAN HESS.—We give normal saline or Ringer's solution, preferably the latter subcutaneously in a very considerable number of our babies, especially those difficult to feed because of a respiratory or cardiac difficulty. It is often necessary to take our babies off their feedings because of cyanosis. We put nothing in the peritoneal cavity but blood, and that infrequently.

Another type of case, which may help to answer your question in which we starve and use larger amounts of fluid are those with diarrhea, not necessarily serious cases of diarrhea. We starve our babies with diarrhea the minute they show anything that might be classified as a true diarrheal state, starving them for at least twenty-four hours and as long as thirty-six. In such cases you must use fluids subcutaneously.

We used to have a lot of cases of suppurative otitis and a considerable number of cases of mastoiditis in the earlier years, but mastoiditis cases in the last four years have been unknown to us and we have very few cases of suppurative otitis. That is probably in large part due to the improvement of the ward technic and possibly to the fact that when our nurses have sore throats or rhinitis we make them stay out of the wards, also we do not open ears, except most infrequently when it is done by an otologist or the resident on the service. We have also reduced spinal punctures to a minimum.

Since we have stopped most operative procedures on these babies, we have had fewer complications. We are inclined to overdo working with these babies. Artificial respiration is a very exceptional thing since we introduced oxygen. I think one of the greatest dangers is overmanipulation in all its forms. We have discarded the Drinker apparatus as impractical for premature infants.

DR A B GROSSMAN (CLEVELAND, OHIO)—I should like to ask Dr Clifford what method of induction of labor they have found to be most successful. I am particularly interested to hear that your results from cesarean operation have not been very satisfactory. I should like to know what other method you find to be better.

DR CLIFFORD—An obstetrician told me two years ago that there were three things they needed in obstetrics. One was a method of eliminating the pain in labor, one was a method of knowing the size of the baby prior to birth, and a third was the method for the induction of labor.

Although I can't speak as an obstetrician, the usual routine in our hospital is to try castor oil first, if that doesn't succeed, the membranes are ruptured, and if that doesn't succeed, a bag is introduced.

CHAIRMAN HESS—Dr Clifford, have you had any experience with the carbon dioxide oxygen?

DR CLIFFORD—We think it is best to give carbon dioxide and oxygen when a respiratory stimulant is needed. In the cyanotic baby certainly there is no lack of carbon dioxide, and oxygen alone is all that is needed.

Will you state specifically what you and Dr Wagner have already implied concerning the mental progress of premature infants? Do you feel, provided that the premature baby is not delivered to your nursery with an intracranial hemorrhage, that it has as good a mental outlook as any other normal baby?

CHAIRMAN HESS—With a few exceptions, where something else might enter in, such as congenital heart disease or some other condition that might interfere with the progress of that child. Potentially, they are normal infants.

DR WAGNER—Or congenital brain defects.

DR CLIFFORD—We would rather see a baby with intracranial hemorrhage die than live and be mentally deficient. We should concentrate on trying to reduce the number of intracranial hemorrhages we see in the newborn babies.

I think it may be of interest, in light of what Dr Wagner has brought out, to have on record the statistics Dr Thomas Goethals has compiled for breech deliveries at the Lying In Hospital. He has reviewed 1,000 breech deliveries, and in the last three years he has taken a personal assignment of all breech deliveries. Among other things, he has compared the statistics, corrected so that they are comparable, of the Lying In Hospital and various other obstetrical hospitals all over the country. When the statistics are so corrected, the breech mortality is just about the same whether the deliveries are made in Philadelphia, Boston, or Chicago.

When he took his cases and classified them according to the infant's birth weight, he found the premature infant, comprising only one-fifth of his total series, contributed one-half of his breech mortality. It is fair to assume that the vast majority of the pathologic findings in those premature breech deliveries were intracranial hemorrhages.

Therefore, when a premature baby presents by the breech, either a manual external version and delivery by vertex or even a cesarean section may be indicated because of the danger of intracranial hemorrhages and later mental deficiency should the child survive.

CHAIRMAN HESS—Our figures show a trend in the same direction, our twenty six breech deliveries with a mortality of six. I don't know how many didn't live long enough to get to our station.

DR. CLIFFORD—It certainly is evident that the interest of both pediatricians and obstetricians all over the country is being concentrated on this particular subject, and I think it is going to be reflected in our national statistics before very long.

CHAIRMAN HESS.—Dr McKitterick has had experience with at least one premature that I know about, and I wonder if he has any ideas he would like to tell us about. Do you remember what that baby weighed?

DR. J. C. MCKITTERICK (BURLINGTON IOWA)—Two pounds three ounces. Aside from the fact that she is very superior mentally, she requires during the winter almost constant administration of liver and iron. Apparently she never has developed her hematopoietic functions to the point they should be. She is now about nine years old.

DR. B. M. KEMPTON (SAGINAW, MICH.)—I would like to ask what the feeling is with regard to the use of pituitrin in obstetric procedure.

DR. CLIFFORD—It is a very powerful agent and has to be used in skilled hands. Passed out indiscriminately, it is a very dangerous therapeutic procedure. Under control it is of very great value in speeding delivery. The premature infant is exposed to two hazards during delivery: trauma, which we have concentrated on, and the other an even greater hazard, intrauterine asphyxia. If the placenta begins to separate or if the baby has his oxygen supply cut off in utero by any other means and suffers intrauterine asphyxia, he attempts to breathe in utero, fills his lungs with amniotic fluid and usually either is stillborn or dies very shortly after birth.

CHAIRMAN HESS.—There is one thing worth emphasizing from the obstetric standpoint. We believe that allowing the cord to pulsate for at least two or three minutes after birth if the baby can be properly protected, is of very great value to the baby.

DR. CLIFFORD—That is a point that is very difficult to settle, some hospitals routinely insist that the cord stop pulsating before it is cut. It has been the routine in our hospital to clamp it off as soon as the baby is delivered. It has been suggested that the reason the babies in cesarean section do so poorly, is that the cord is not allowed to stop pulsating and to empty its volume of placental blood into the fetus. All that has to be investigated. Certainly, some obstetric writers have explained the apparent discrepancy in the data on the blood of the newborn on that basis. That is, if you do not clamp the cord and wait until it stops pulsating you may get a polycythemia and quite severe icterus neonatorum in the course of the first two or three days. If you clamp the cord immediately, the blood count at birth will be approximately four million, no polycythemia, and you will encounter a very low incidence of icterus neonatorum. There is supposed to be an 80 per cent reduction in the incidence of severe icterus neonatorum when the cord is not allowed to stop pulsating.

DR. KEMPTON—Is alphalobelin a good product?

CHAIRMAN HESS.—We did some experimental work with it, and then also had occasion to use it over a period of something like six months, six or seven years ago when it first came into general use. We are very much afraid of it.

DR. CLIFFORD—Resuscitation in the newborn is a problem of greater importance today than it was a number of years ago.

Dr Frederic C Irving in a very extensive survey took five hundred district deliveries and investigated the records of resuscitation. He found that 90 per cent of the babies cried the minute they were born. The only anesthesia the mothers had received was "bulgarian" and a few kind words. They had their labor without the help of any drugs whatsoever. When he investigated the so called twilight sleep series, when morphine and scopolamine were used, he found that 60 per cent of the babies had to be resuscitated as opposed to 10 per cent in the first mentioned series. With the present analgesia that is being used, which is pentobarbital or nembutal with or without scopolamine, 40 per cent of the babies had to be resuscitated. The obstetricians expect it and take that into consideration as the price paid for analgesia.

This change in obstetric practice has changed the pathology of diseases of the newborn. When the mother was conscious of her labor and was becoming exhausted, when the obstetrician was conscious of the mother's suffering, and when labor was long and drawn out, there was a tendency to shorten the last stage of labor and deliver instrumentally with its resultant increase in intracranial hemorrhage. Now, with the mother completely free from pain and out of the picture, the cervix can be allowed to dilate to its full extent and labor take its normal course. The incidence of midforceps and high forceps deliveries in our hospital has been reduced to practically zero since the advent of successful analgesia. The incidence of intracranial hemorrhage is now so low we have difficulty in finding a case to show the students. Thus, the change in obstetric practice has eliminated intracranial hemorrhage to a large measure, but it has substituted asphyxia and the problem of resuscitation. The mortality and morbidity are lower under the present routine and therefore it is a fair exchange.

DR GROSSMAN—Does avertin have any effect on the child?

DR CLIFFORD—It stops labor immediately.

DR KEMPTON—Have you seen any difficulty with sodium amytal?

DR CLIFFORD—You may not have heard of the research Dr Irving has conducted on these various analgesics. He took 100 patients in each series. To the first he gave pentobarbital and scopolamine, to the next he gave sodium amytal alone or in combination with something else, to the next, avertin, and so forth. He found that sodium amytal was good, but that pentobarbital with or without scopolamine and rectal ether was better. There were less failures as far as analgesia was concerned, there was less excitement on the part of the mothers, and the babies showed less need for resuscitation.

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES

SOCIAL SERVICE SUPPLEMENTARY REPORT GENERAL SUMMARY

Dr Clifford G. Grulee Chairman Dr Murray H. Bass Dr L. R. DeBuys Dr Roger H. Dennett Dr Henry Dietrich Dr Lewis Webb Hill, Dr George F. Munns.

SOCIAL SERVICE

THIS report includes not only the original thirty-five hospitals but also three which are included in a supplementary report.

Of the thirty-eight hospitals thirty-five have social service departments (Table I). One has no social service department; one carries on social service work but not as a separate department; one failed to reply. Among those in charge of social service work only seven indicate that they have had definite social service training. This department is conducted in sixteen instances by nurses, in one instance by a physician and in seven instances by individuals having college degrees. In five instances no reply to 'qualifications' was given. It is surprising that only one-fourth of the replies indicate that those in charge of the social service work have had special training. Physicians and nurses are no more qualified for the direction of social service work unless they have had special training than social service workers are qualified for nursing or medicine.

In each of the thirty-five hospitals the social service worker is a full-time worker. The number of social service workers in the respective departments varies from one to fourteen, the usual number being from two to four. In only four instances are these part-time workers.

Sixteen hospitals investigate all patients who come to the hospital; two investigate all except private cases; two investigate only free and part-pay patients. Thus, twenty hospitals investigate practically all their patients since the number of private patients is so few as to be negligible in most of these hospitals.

In thirty-one of the hospitals interviews with parents are held; eight investigate the homes in all cases; and twenty-four in special cases. One even provides monthly home visits. In ten instances the hospital social service investigates the ability of the patients to pay, while twelve make no such investigation. Two investigate by special social service workers; three by the admitting officer; one, by the judge of the county; and three on free cases only.

As to case history taking, nineteen take a social history in all cases; twelve file this social history with the medical history; two file part of it; two, a summary; and one by request. Eighteen file their social histories with the bedside notes, and in twenty-two hospitals and abstracts are filed with the history of the case.

Concerning convalescent care (Table II) the social service arranges for this care in twenty-six hospitals; among others only in some cases and in five not at all. Twenty-nine hospitals have convalescent institutions available; in one a small charge is made. Twenty-six have foster homes; one for pay patients only. In twelve

TABLE I

HOSP	WORKER IN CHARGE		WORKERS		PATIENTS INVESTIGATED				SOCIAL HISTORY			
	QUALIFICATIONS	FULL TIME	NUMBER	FULL TIME	ALT	HOSP INTERVIEW WITH PARENT	HOME INVESTIGATED	ABILITY TO PAY	TAKE ON ALL	FILED WITH MEDICAL HISTORY	ADMT WITH BEDSIDE NOTES	FILED WITH HISTORY
1	Yes	Yes	4	Yes	Yes	Yes	S C	No	No	No	No	No
2	Yes	Yes	3	Yes	Yes	Yes	S C	Yes	Yes	No	H req	--
3	Yes	Yes	2	Yes	F & P P	Yes	S C	Yes	Somo	No	Yes	Yes
4	Yes	Yes	4	Yes	No	Yes	S C	Spec S S	Yes	No	Yes	Yes
5	Yes	Yes	1	Yes	No	Yes	S C	No	Yes	Yes	Yes	Yes
6	Yes	Yes	7	Yes	ox P C	Yes	S C	Spec S S	Yes	No	Yes	Yes
7	Yes	Yes	3	Yes	--	Yes	S C	No	No	Yes	Yes	--
8	Yes	Yes	23	Yes	No	Yes	S C	Co judgo	No	No	No	No
9	Yes	Yes	3	Yes	No	Yes	S C	No	No	No	Yes	Yes
10												
11	No											
12	Yes	Yes	10	Yes	No	Yes	S C	Admit officer	No	Yes	Yes	Yes
13	Yes	Yes	2	No	Yes	Yes	Yes	Free only	Yes	Yes	Yes	Yes
14	Yes	Yes	5	Yes	No	Yes	S C	No	No	Sum	Yes	Yes
15	Yes	Yes	8	Yes	Yes	Yes	S C	---	Yes	No	Yes	Yes
16	Yes	Yes	12	Yes	No	Some	No	No	No	By req	No	By req
17	Yes	Yes	0	--	No	--	--	Free only	No	--	--	--
18	Yes	Yes	9	No	No	Some	S C	Yes	No	No	Yes	Yes
19	Yes	Yes	2	Yes	No	Yes	S C	No	Yes	No	No	No

TABLE I—CONT'D

HOSP	p	WORKER IN CHARGE		WORKERS		PATIENTS INVESTIGATED					SOCIAL HISTORY			
		QUALIFICATIONS	FULL TIME	NUMBER	FULL TIME	ALL	HOSP INVESTIGATIVE WITH PARENT	HOME INVESTIGATED	ABILITY TO PAY	TAKEN ON ALL	FILED WITH MEDICAL HISTORY	ABST WITH BEDSIDE NOTES	FILED WITH HISTORY	
20	Yes	G.N.	Yes	2	Yes	Yes	Yes	B.C.	No	Yes	Yes	Yes	Yes	
31	Yes	G.S.S.*	Yes	3	Yes	Yes	Yes	Yes	No	Yes	No	No	No	
23	Yes	G.N.	Yes	--	Yes	Yes	Yes	B.C.	No	Part	Yes	Yes	Yes	
23	Not			4		Yes	Yes	B.C.	B C	Yes	Yes	No	--	
24	Yes	R.N.	Yes	3	Yes	Yes	Yes	B.C.	Free only	Yes	Yes	--	Yes	
25	Yes	A.B.	Yes	4	No	Yes	Yes	B.C.	Yes	Yes	No	Yes	Yes	
28	Yes	G.S.S.	Yes	2	Yes	Yes	Yes	B.C.	B.C.	No	Yes	Yes	Yes	
27	Yes	R.S.	Yes	2	Yes	No	Yes	B.C.	Admit officer	Yes	No	Yes	Yes	
28	Yes	R.N.	Yes	2	Yes	Yes	Yes	B.C.	Yes	Yes	Yes	No	Yes	
29	Yes	M.D.	Yes	14	Yes	No	Yes	B.C.	Admit officer	Yes	No	H rep	Yes	
30	Yes	A.B.	Yes	1	Yes	F & P	Yes	B.C.	Yes	Yes	No	No	Yes	
31	Yes	R.N.	Yes	2	Yes	ex. P O	Yes	Yes	Yes	Yes	Part	Part	Yes	
32	Yes	R.N.	Yes	8	Yes	No	Yes	B.C.	Yes	Yes	Yes	No	No	
33	Yes	R.N.	Yes	3	Yes	Yes	Yes	--	No	No	--	--	--	
34	Yes	R.N.	Yes	5	Yes	--	Yes	--	No	below	2 years	Yes	Yes	
35	Yes	R.N.	Yes	1	--	Yes	Yes	Yes	Yes	Yes	Sum	Yes	Yes	
36	Yes	R.N.	Yes	4	No	No	Yes	B.C.	No	No	N pay	No	--	
37	Yes	T.S.R.	Yes	3	Yes	Yes	Yes	B.C.	Yes	Yes	Yes	Yes	Yes	
38	Yes	G.S.S.	Yes	5	--	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	

For unmarried mothers and babies.

†Not a separate department.

Abbreviations used: A sup., assistant superintendent; B mtrs board of managers; By req by request; C H N city health nurse; D S.S. director of social service; ex P except private cases; Facit, aged facilities adequate; F & P P free and part pay; Fin. financial; G S.S. graduate social service worker; H rep home report; if sec. if necessary; Lim. limited; M H medical history; N pay neuropsychiatry; Occ. occasionally; Reg. regular worker; S.C. special cases; Spec S.S. special social service worker; Sum summary; Sup Superintendent; T S.S. trained social service worker.

instances arrangements for convalescent care are adequate, while in twenty one they are not, and one answered "fair." Concerning the follow up of cases, twenty six follow up all cases, while nine follow up cases as indicated by the need or desire to do so. In thirty six instances, the social service workers assist in returning the patients for further hospitalization if that is necessary.

TABLE II

HOSP	CONVALESCENT CARE BY S S						FOLLOW UP	RE CALL	VOLUNTEERS			
	AR RANGE	CONV INST		FOSTER HOMES		FACIL. ADEQ			INDOOR		OUTDOOR	
		AVAIL	USE	AVAIL	USE					NO		NO
1	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	--	Yes	1
2	Yes	Lim	Yes	Pay	patients	No	Yes	Yes	Yes	4	Yes	2
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	5	No	--
4	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	30	Yes	2
5	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	--	No	--
6	Yes	Lim	Yes	Lim	Yes	No	Yes	Yes	Yes	85	Yes	6
7	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	4 5	No	--
8	Yes	Yes	Yes	Lim	Yes	No	Some	Yes	Yes	--	No	--
9	Yes	Yes	Yes	Yes	Yes	Yes	Some	Yes	Yes	1	--	--
10												
11		Yes										
12	Yes	Yes	Yes	No	--	No	Yes	Yes	Yes	7	Yes	3
13	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	--	No	--
14	Yes	Yes	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	2	Yes	2
15	No	Yes	Yes	No	--	Yes	Yes	Yes	Yes	1	Yes	--
16	Yes	Lim	Yes	Some	Yes	No	Yes	Yes	Yes	--	Yes	--
17	No	No	--	No	--	None	Yes	Yes	No	--	No	--
18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	5	Yes	5
19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	--	No	--
20	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	3	Yes	5
21	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	3	Yes	3
22	Yes	Yes	Yes	No	--	Yes	Yes	Yes	No	--	No	--
23	Yes	Yes	Yes	No	--	Fair	S C	Yes	Yes	1	Yes	1
24	No							Yes	No	--	No	--
25	Some	No	--	Yes	Some	No	Some	Yes	Yes	3	Yes	1
26	Yes	Yes	Yes	Lim	Occa.	Yes	Yes	Yes	Yes	3	No	--
27	By req	Yes	Yes	Yes	Some	No	Yes	Yes	Yes	1	No	--
28	No	Yes	Yes	Yes	Yes	No	Some	Yes	Yes	20	Yes	12
29	Yes	Some	Yes	Some	Some	No	Yes	Yes	Yes	56	Yes	12
30	Yes	Yes	Yes	Yes	Yes	No	If nec	Yes	Yes	15	No	--
31	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	--	Yes	30
32	Some	Yes	Yes	Yes	Yes	Yes	Some	Yes	Yes	26	Yes	10
33	Yes	Yes	Yes	No	--	Yes	Yes	Yes	No	--	Yes	2 3
34	By req	--	--	--	--	Yes	Yes	Yes	Yes	2 3	Yes	--
35	No	No	--	Yes	Yes	No	Yes	Yes	No	--	--	--
36	Yes	No	--	Yes	Yes	No	By req	Yes	Yes	--	Yes	--
37	Some	Some chg		No	--	No	If nec	Yes	Yes	1	Yes	3
38	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	--	--	--

*Except diabetic and cardiac.

Twenty five departments use volunteers indoors, and eleven do not. The number of workers varies from one to eighty five, the usual number being four. Twenty one employ volunteers outdoors, and twelve do not. The number varies from one to thirty, the usual number being three.

In twenty five instances the social service is supported by hospital funds (Table III), in five, by outside funds, and in five, partly by the hospital and partly by outside funds. Twenty two have a lay committee in charge of social service, ten have a physician on this committee. In twenty two instances, the social service is represented on the board of managers.

Thirty four of the thirty-eight hospitals have social service workers in the dispensary (Table IV); the number varies from one to twenty, the usual number being two. In only six hospitals are the workers for the dispensary only. In eighteen instances all new cases are seen by social service workers; in nine those selected by the physician and in six only special cases. Nineteen take a social history on all patients, fourteen send all such histories taken to the physician. In two instances this is done by request only, and in one instance only a summary is sent. In fourteen instances only the important case histories are sent to the physician,

TABLE III

HOSP	S. S. SUPPORT		COMMITTEE IN CHARGE		
	HOSP FUNDS	OUTSIDE FUNDS		PHY ON	REP ON B MGRS
1	Yes	No	Yes	No	Yes
2	Yes	No	Yes	3	Yes
3	Yes	--	Yes	No	Yes
4	No	Yes	Yes	No	Yes
5	Part	Part	No	--	--
6	No	Yes	Yes	No	Yes
7	Yes	--	Yes	Yes	Yes
8	Yes	No	Yes	1	Yes
9	Yes	No		Hosp officers	
10					
11					
12	Part	Part	No	--	--
13	Yes	No	No	--	--
14	Yes	--	Yes	Yes	Yes
15	Yes	--	Yes	--	Yes
16	Part	Part	No	No	No
17	Yes	--	No	--	--
18	No	Yes	Yes	Yes	Yes
19	Part	Part	Yes	1	Yes
20	Part	Part	Yes	No	Yes
21	Yes	--	Yes	1	Yes
22	No	Yes	Yes	No	Yes
23	--	Yes	No	--	--
24	Yes	No	No	No	No
25	Yes	No	No	--	--
26	Yes	No	Yes	1	Yes
27	Yes	No	Yes	2	Yes
28	Yes	No	No	--	--
29	Yes	No	Yes	Yes	Yes
30	Yes	--	Yes	No	Yes
31	Yes	No	Yes	No	Yes
32	Yes	No	Yes	No	Yes
33	Yes	No	No	No	No
34	No	Yes	No	--	--
35	Yes	No	Yes	No	Yes
36	Yes	No	No	No	No
37	Yes	No	No	--	--
38	Yes	--	Yes	No	Yes

four give verbal reports, and two give verbal reports if requested. Eighteen file the social history with the clinical record, one files a summary and one files part of a history. Twenty three keep a separate file for social histories, and twenty seven keep these histories in a permanent file.

Twenty nine departments make home visits, two occasionally and in one instance the city health nurse makes the home visits. In twenty nine instances these home visits are made to check conditions, and in two cases they are occasional. Twelve make calls to check ability to pay two occasionally and one on free cases only.

TABLE IV

HOSP	SS	WORKERS		NEW CASES		SOCIAL HISTORY						SS HOME VISITS		
		NUMBER	DISP ONLY	ALL SEEN BY SS	HOW SELECTED	SENT TO PHYSICIAN			FILED			MADE	CHECK CONDITIONS	CHECK ABILITY TO PAY
						TAKEN	ALT	VERY IMP	VERBAL REPORT	WITH CLINIC RECORD	SEPARATE FILE			
1	Yes	4	No	No	Phy	Fin	No	No	By req	No	Yes	Yes	Yes	No
2	Yes	4	Yes	Yes	--	Yes	No	Yes	--	No	Yes	Yes	Yes	Yes
3	Yes	3	No	No	S C	No	No	Yes	Yes	No	Yes	Yes	Yes	No
4	Yes	2	No	No	Phy	No	Yes	--	--	Yes	--	Yes	Yes	No
5	Yes	7	No	Yes	--	Yes	No	No	--	No	Yes	Yes	Yes	Occn
6	Yes	2	No	No	S C	No	Yes	--	--	Yes	Yes	Yes	Yes	No
7	Yes	2	No	No	S C	No	Yes	--	--	Yes	Yes	Yes	Yes	No
8	Yes	2	No	No	Phy	No	Yes	--	--	Yes	Yes	Yes	Occn	No
9	Yes	1	No	Yes	--	No	No	Yes	No	No	Yes	Yes	Occn	No
10	Yes	1	No	Yes	--	No	No	Yes	No	No	Yes	Yes	Occn	No
11	Yes	10	No	No	S C	Yes	Yes	--	--	Yes	No	--	Yes	No
12	Yes	13	No	Yes	S C	No	No	Yes	No	No	Yes	Yes	Yes	No
13	Yes	3	Yes	No	Phy	No	No	--	Yes	No	Yes	Yes	Yes	No
14	Yes	6	No	No	S O	Yes	No	--	No	No	Yes	Yes	Yes	No
15	Yes	1	Yes	No	--	No	No	Yes	No	No	Yes	Yes	Some	No
16	Yes	1	No	No	--	No	By req	--	--	No	Yes	Yes	No	--
17	Yes	1	No	No	Phy	No	No	Yes	--	Yes	No	No	Yes	Yes
18	Yes	20	No	Yes	--	Yes	No	Yes	By req	No	Yes	Yes	Yes	Occn.
19	Yes	6	No	Yes	S C	No	By req	Yes	No	No	Yes	Yes	Yes	Yes

TABLE IV--Cont'd

HOPE	R. B.	WORKERS		NEW CASES		SOCIAL HISTORY						8 & HOME VISITS			
		NUMBER	DISP ONLY	ALL SEEN BY R. B.	HOW SKETCHED	SENT TO PHYSICIAN			FILED			MADE	CHECK CONDITIONS	CHECK ABILITY TO PAY	
						ALT	VERY IMP	VERBAL REPORT	WITH CLINIC RECORD	SEPARATE FILE	PERMANENT FILE				
20	Yes	1	No	No	Phy	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No
21	Yes	--	--	Yes	--	Yes	--	--	--	Yes	Yes	Yes	--	--	Free
22	Yes	--	--	Yes	--	Yes	Yes	--	--	Part	--	Yes	Yes	Yes	--
23	Yes	2	No	Yes	--	Yes	Yes	--	--	No	Yes	Yes	Yes	Yes	Yes
24	Yes														
25	Yes	5	No	Yes	--	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
26	Yes	2	No	Yes	Phy	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
27	Yes	23	No	Yes	--	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
28	Yes	2	No	Yes	--	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
29	Yes	8	Yes	Yes	--	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
30	Yes	2	Yes	Yes	--	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
31	Yes	2	No	Yes	--	Yes	Yes	--	--	Yes	Yes	Yes	Yes	Yes	Yes
32	Yes	8	No	No	--	No	Yes	--	--	Yes	Yes	Yes	Yes	Yes	Yes
33	Yes	3	No	No	--	No	No	Yes	No	Yes	--	Yes	Yes	Yes	No
34	Yes	5	No	No	S.C.	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
35	Yes	1	No	Yes	Phy	No	Yes	--	--	Yes	No	Yes	Yes	Yes	No
36	Yes	3	No	Yes	--	Yes	Yes	--	--	Yes	No	Yes	Yes	Yes	Yes
37	Yes	2	Yes	No	Phy	Yes	Sum	--	--	Sum	Yes	Yes	Yes	Yes	No
38	Yes	6	No	No	--	Yes	Yes	--	--	Yes	Yes	Yes	Yes	Yes	Yes

Twenty seven use volunteers in the social service (Table V), the number varies from one to ninety one, eighteen have twenty or less and these work from one half to six days per week for the fifteen dispensaries which reported. Only five have irregular attendance. In twenty four instances these workers are trained as follows: seventeen, by the director of social service, two, by the head nurse, two, by a regular worker, one, by the superintendent, and one, by the assistant superintendent. In one instance no training is given. In twenty three instances, these volunteers are said to be satisfactory. In the one case in which they are said to be not satisfactory, they are not trained. In one instance the work is said to be fair, and in one, the volunteers have been introduced too recently for a report to be made. The work of the volunteers is as follows: In nine dispensaries they assist the doctors and nurses, in sixteen they do clerical work of typing and filing, in seven they do follow up work, and in ten they take histories on the patients. In seven they form the motor corps, in four they help with the occupational therapy, and in fourteen they do reception room work. In four they work in the record room, one runs errands, in eleven they do secretarial work, one does social case work, and in three they take care of supplies.

Summary

If there is one place where social service work would seem to be necessary, it is in a children's hospital, it is interesting to note how generally the children's hospitals in this country and Canada are aware of the fact. It is peculiar, however, that they have not considered it necessary to employ persons specially trained in social service work in so many instances. Only 20 per cent of them have such service. However, the social service worker is, practically in all instances, a full time worker. We find it impossible to judge whether the number is adequate from the figures given.

The extent of investigation of patients by the social service seems to vary somewhat with respective local conditions, but generally the situation seems to be ably handled. In comparatively few, however, is the ability of the patients to pay determined by the social service worker.

There is considerable variation in types of social histories and in the disposition of these. On the whole, there seems to be adequate cooperation with the medical staff with respect to the social histories in these hospitals.

It is surprising that such a large number of hospitals have convalescent care for their children, but it is not surprising that in most instances the available beds are inadequate. Only in recent years has convalescent care of hospital patients begun to receive the amount of attention which it deserves, perhaps partially because of the fact that it is so much cheaper to care for a convalescent in a convalescent home than in a hospital. Foster homes are used in many instances, and here too the service is inadequate to meet the need. The follow up of these cases is quite satisfactory, and in every instance the social service is used for recall of patients to the hospital.

Volunteers are employed in practically all of the hospitals. They are employed both indoors and out and are assigned to various duties, such as maintenance of libraries, occupational therapy assistance, assistance in recording and caring for histories and records, transportation for patients, etc. The support of the social service is in most instances by the hospital itself though in some instances it is carried on by outside agencies. It is a surprising fact that in only ten instances is there a physician on the board in charge of social service. This would seem to be a strange oversight on the part of those in charge of social service and should be corrected.

TABLE V

HOSP	VOLUNTEERS						WORK											
	USED	NUMBER	DAYS PER WEEK	IRREGULAR ATTENDANCE	TRAINED BY	SATISFACTORY	ASSIST	CLERICAL	FOLLOW UP	HISTORIES	MOTOR CORPS	OCCUPATIONAL THERAPY	RECEPTION	RECORD ROOM	RUN ERRANDS	SECRETARIAL	SOCIAL CASE WORK	SUPPLIES
1	Yes	40	6	No	D S S	Yes				*			*					
2	Yes	4	12	No	H N	Yes										*		
3																		
4	Yes	28	--	No	D S S	Yes					*	*		*			*	
5	No																	
6	Yes	91	--	--	D S S	Yes					*							
7	Yes	12	2	Yes	D S S	Yes	*											
8																		
9	No																	
10	No																	
11																		
12	Yes	10	6	No	D S S	Fair	*	*										
13	Yes	52	--	No	D S S	Yes	*	*	*				*			*		
14	Yes	7	6	No	H N	Yes	*						*		*			
15	Yes	3		Yes	D S S	Yes							*					
16	No																	
17	No																	
18	Yes	15 20	2	No	D S S	Yes	*	*	*					*				
19	Yes	40	6	No	D S S	Yes	*	*					*					*
20	Yes	4	--	Yes	--	Yes		*	*									*
21																		
22	Yes	20																
23	Yes	2	3		Reg W	Yes	*	*					*					
24																		
25	Yes	3	1½		Reg W	Yes	*						*					
26	Yes	2	3	No	D S S	Yes												
27	Yes	1		No	D S S	Yes				*								
28	Yes	4		No	D S S	Yes					*			*				
29	Yes	14	6	No		Yes	*	*								*		
30	Yes	6	2	Yes	D S S	Yes	*									*		
31	Yes	3	½	No	D S S	Yes												
32	Yes	36	--	--	D S S	Yes	*	*	*				*			*		
33	Yes	10	--	Yes	No	No										*		
34	Yes	17	2	No	D S S	Yes	*	*			*							*
35	No																	
36	Yes	50	--	--	A. sup	Yes	*			*	*	*	*	*	*	*		
37	Yes	25	1	--	D S S	Yes												
38	Yes	30	-	No	Sup	Yes					*	*				*		

The social service in the dispensaries of these hospitals is carried on very much the same as it is in the hospital, both as to social histories and home visits. The volunteer work is quite extensive, but the type of work assigned to volunteers is most varied.

SUPPLEMENTARY REPORT

THREE HOSPITALS OMITTED IN THE ORIGINAL REPORT

Three children's hospitals omitted in the original survey are considered in the following report. These hospitals are located in Oregon, Texas, and Pennsylvania. In the combined reports thirty eight children's hospitals in this country and Canada are considered.

Professional Staff—Patients in the wards are under the exclusive care of physicians appointed to the attending staff in each hospital.

Two hospitals have specialists on the attending staff in all specialties considered in the original report, one lacks an attending psychologist and a specialist in oral hygiene. In one instance the specialists visit at regular intervals, in the case of the other two they are often "on call" only. In one instance the medical director is employed full time, otherwise there are no full time physicians on the attending staff, and none receive a salary except in one instance in which the pathologist, roentgenologist, and dentist are paid a salary. The attending staff has duties in the dispensary in each hospital.

House Staff—Among the house staffs these hospitals report four, three, and one residents, respectively. Each one serves for one year and has definite dispensary duties. One hospital requires preliminary training of at least one year of pediatric internship, two require only one year of rotating internship. The salaries are respectively \$100.00, \$75.00, and \$40.00 per month. Women are not eligible for the residency in one hospital. Only one employs an assistant resident. In this instance one year of preliminary general internship is required. The length of the service is one year, women are eligible and the salary is \$40.00 per month.

One hospital employs no internes but has four residents. The other two hospitals employ two and eleven internes, respectively. In both of these hospitals women are eligible. Salaries are \$25.00 and \$17.00 per month. Internships are open to graduates of class A schools. The length of the service is one year in each, and in both hospitals the interne has duties in the dispensary.

Two of the hospitals are connected with a medical school, the third affords opportunity for study to postgraduate students. Clinics and ward rounds for students are held in each hospital. These are also open to practicing physicians. One hospital has a definite course of postgraduate instruction.

Clinical and pathologic conferences are held regularly in two hospitals, these occur once weekly. One institution has no pathologic conferences.

The two hospitals employing internes afford them special instruction in x-ray work and in the pathologic, bacteriologic, and serologic laboratories. This instruction is chiefly in diagnosis. There is no special instruction in physiotherapy except in one instance where it is available if the interne is especially interested. Neither hospital affords special instruction in diet and nutrition other than that available on any general medical service.

Medical libraries and facilities for research are available in each hospital.

One hospital does not have observation wards, instead, individual rooms are used for isolation in suspected contagion.

Routine blood counts, urinalyses, histories, physical examinations, vaginal smears, von Pirquet or Mantoux tests, and Wassermann and Kahn tests are performed before admission to the wards in one hospital, one omits the von Pirquet and Wassermann tests. Only one takes routine throat cultures for *B. diphtheria*. One hospital did not reply to this portion of the questionnaire.

Two hospitals send special cases such as pneumonia, acute upper respiratory infections, impetigo, erysipelas, etc., to the general wards but use the isolation room system if precaution is indicated by the particular case. One does not admit gonorrheal vaginitis, two do not admit gonorrheal ophthalmia. One hospital did not reply to this section of the questionnaire.

Superintendent's Section.—Each hospital is located in a residential district—one, in a quiet good district one in a noisy poor district, and one, in a moderate district. None of them have playground facilities in the grounds of the hospital.

The respective bed capacities are seventy five eighty two, and seventy five, including cribs and bassinets. The age limit for patients in two hospitals is fourteen years, and in one there is no age limit (probably refers to general hospital with which it is associated). Two have special wards for medical and surgical cases only, none have special neurologic wards, only one has special wards for otolaryngologic cases. None have special wards for contagious cases.

Some types of illness are excluded in each hospital. One excludes pulmonary tuberculosis contagious diseases and acute infectious venereal diseases. A second excludes tuberculosis, chronic mental cases, and contagious diseases unless the patient can afford a day and night nurse. The third excludes primary syphilis, gonorrhea and active tuberculosis, impetigo, scabies, and the contagious diseases. Only one maintains a ward for contagious diseases.

The total number of patients admitted to each hospital in 1932 were 2,228 9,635 and 2,235 respectively. In the same order hospital deaths were 73, 280 and 111. All hospitals accept both colored and white children. They are segregated in one hospital. One hospital does not have private rooms for children the other two have nine and eighteen respectively.

One hospital derives 96 per cent of its funds from the state, the remainder from patients, one from the state (33 1/3 per cent) endowment, community chest and patients one does not reply. The cost per patient per day in the respective hospitals is \$4.58 \$4.82 and \$3.50.

The superintendent is a physician in one hospital a registered nurse in the second and a layman, in the third.

Nursing.—Only one hospital maintains its own complete nursing school, the course is for three years, and the average number of student nurses is 117. However, the other two hospitals afford instruction to affiliates from other schools. The section of the questionnaire concerning the number of duty nurses assigned to various wards and the length of their assignments and proportion of number of nurses to patients was not answered in two of the questionnaires. The third indicated that the proportion of nurses to patients is sufficient for efficient care.

Operating Room.—The operating rooms are in charge of experienced graduate nurses in each hospital. The number of operations in the last fiscal year was 1,691 6,419 and 1,781, respectively.

Student nurses are given instruction in the preparation of infant foods in each hospital. The length of the assignments in the respective hospitals are five four teen and thirty days. Two hospitals afford instruction in the preparation of children's diets, the length of the respective assignments in each course being five and fourteen days. Two hospitals afford all nurses practical experience in the social service department. This is two weeks assignment in one and a month's assignment in the other institution.

Student nurses are not assigned to night duty in one hospital the other two permit them to go on night duty during the latter part of the first year.

A graduate nurse is in charge of the wards during the day in each hospital. Student nurses serve in this capacity at night in two of the hospitals. Supervising nurses are also employed in each hospital, the number being five, ten, and one, respectively.

The total number of hours devoted to classroom, laboratory, and demonstration work is sixty hours for the three month affiliate course in one hospital, 489 hours for the three year affiliate course in the second, and 803 hours in the third hospital which maintains its own complete school. Although one hospital does not have its own complete nursing school, through cooperation with a university group a three year course in pediatric nursing is available.

Postgraduate instruction in pediatric nursing probably is available in each hospital although none of them states that there is a definite course in that type of instruction.

None train nursery maids, none afford opportunity for training in an affiliated nursery school or kindergarten, and none use "ward helpers" on any wards.

Separate towels, thermometers, and wash cloths are provided for each infant and child in all hospitals except one which does not provide a separate thermometer for each older child. In all hospitals separate gowns are provided for handling each baby and used only for that baby when "deemed advisable" or in infected cases. Ordinary isolation technique is used in all hospitals to prevent cross infection.

X ray Facilities—Each hospital has x ray diagnostic facilities although in one instance the x ray department of another hospital four blocks distant is used. Full time technicians are employed in each department, and the facilities of the respective departments are available at any time during the day or night. All departments are equipped for high speed, superficial and deep radiography, and all have a fluoroscope, are able to take stereoscopic plates, and have a portable machine.

Internes do x ray work for one month as part of their regular training in one hospital, in another the work is optional, and in the third it is not available. Two hospitals consider that their x ray equipment is adequate, the third, of course, has no equipment of its own. The hospital x ray departments also serve the dispensary in two hospitals, and outside physicians, in one instance.

The number of x ray plates taken during the last fiscal year were 1,070, 4,122, and 589, respectively. The number of deep and superficial treatments in one instance was eleven, in another 1,403, and in the third there was no reply.

Laboratory Facilities—Each hospital has a director in charge of all laboratory work. In two instances he is a full time director. In one instance he is available only four hours daily.

Pathologic Facilities—Two have full time directors of the pathologic laboratory. Three have full time technicians for the pathologic laboratory. Internes do routine laboratory work in none of the hospitals.

Each hospital considers its facilities adequate for its needs. There are available facilities for research work in two hospitals. The number of autopsies performed as compared to deaths during the last fiscal year was respectively as follows: 50/73, 117/280, and 30(?) /51.

Clinical Laboratory—There are full time directors in two hospitals and full time technicians in three.

In no instance do internes perform routine laboratory work. Blood chemical determinations are done in all laboratories. Satisfactory "fume hoods" and colorim

eters are available in each laboratory and each has satisfactory equipment for basal metabolism tests. Each laboratory reports that it considers its equipment adequate and all have facilities for research work.

Bacteriologic Laboratory—Only one hospital has a fulltime director, all have full time technicians. The internes in no instance do routine bacteriologic work. All have electric incubators, two make their own media and one buys them from a supply house.

Two laboratories keep animals for experimental work. All consider that their laboratory facilities are adequate for their needs; two have facilities for research work.

Serologic Laboratory—There is a full time director in only one instance. All have full time technicians. In no instances do internes perform routine laboratory work. Wassermann and Kahn tests are made in each laboratory. All laboratories consider their equipment adequate for their needs and two provide facilities for research work.

Laboratory (Miscellaneous)—Two have facilities for simple photography and one for color photography. One has facilities for motion picture photography. An electrocardiograph is available in each hospital.

Physiotherapy—All hospitals have facilities for physiotherapy and in each the department is separate. There is a full time director in one department and a full time technician in another. No department has both a full time director and a technician.

All departments have facilities for dry heat, moist heat, massage, ultraviolet light, diathermy and electricity. In each instance they may be used at the bedside.

Diet Kitchen—All have graduate dietitians in charge of the department. The dietitian has entire charge of the menus in two hospitals, but only the special diets in one.

'Standard special diets' are prepared by cooperation of the dietitian and the medical personnel in all hospitals.

Social Service—This is included in the special report along with that of thirty five children's hospitals covered in previous reports.

Occupational Therapy—This activity is lacking or poorly developed in all hospitals.

Education—Schooling is provided for children by a public school teacher in one hospital. In the second this work is done only by volunteer workers and in the third is available only to cardiac patients and is carried on by a university student teacher.

Provision is made for the play activities of convalescents in only one hospital, and in that instance the work is performed only by volunteers.

Dispensary—General Each of the three hospitals not included in the first report maintains an associated dispensary in the same plant with the hospital. One dispensary occupies four floors in the others two each. The dispensary occupies the entire building in each instance. The number of waiting rooms is respectively 6, 8 and 4. The number of examining rooms, sixty-two, six, and ten. One has no isolation rooms.

The average daily clinic attendance in the same order is 425, 150, and 221 persons, and the total attendance for the last fiscal year 20,000, 9,205 and 67,569 persons. Discrepancies appear in the figures reported to us in two instances, for obviously a daily attendance of 425 when the clinic is open six days weekly as it is in each instance, would equal a total of considerably more than 20,000 for the year.

and the same thing is true when attendance figures are reported at 150 daily and 9,205 for the year. New patients in each clinic reported for the last fiscal year are respectively 12,000, 4,311, and 4,988 individuals.

Few cases in any instance come from more than thirty miles away. None are seen only by appointment. All charge a fee of 25 cents for the first visit and 10 or 25 cents for subsequent visits. In each dispensary patients who are able to pay physicians are rejected. Eligibility is determined by social service departments.

Organization. Two dispensaries have medical directors and in each instance, he is directly connected with the associated hospital.

Each dispensary has available specialists in practically all specialties listed in the questionnaire. Pediatricians are in regular attendance in each instance, and general medical clinics are held daily. Specialty clinics are not held daily in any dispensary. Usually they are held once or twice weekly, except in one instance in which the eye clinic is held daily.

Special. The professional staff serves in both hospital and dispensary in two instances, one did not reply. Each dispensary obtains and files case records on all cases, and these clinical records accompany the patient if he is admitted to the hospital.

All refer patients discharged from the hospital back to the clinic for follow up, and the hospital records are available there if they are needed. In only one instance are all cases first seen by the medical department.

In each instance cases suspected of contagion are immediately put into isolation.

Medical students receive instruction in each dispensary. In each instance the dispensary is organized into special clinics, such as cardiac, nephritic, diabetic, tuberculosis, etc., as listed in the original report, and all can offer service in practically all of the usual specialties. Two dispensaries maintain separate clinic sessions for infants.

Laboratory Facilities, Clinical. Two dispensaries use the hospital laboratory. One has its own laboratory but does not consider its facilities adequate.

Blood, urine, and stool examinations and blood chemical analyses may be made in each dispensary. None of the three dispensaries has a special laboratory for serologic or bacteriologic work.

Photographs are taken in the dispensary in one instance. One dispensary has a separate x-ray department but may also use the hospital department. As previously noted these departments are considered adequate for their needs. Two have facilities for physiotherapy in the dispensary.

Nursing. There is a head nurse in charge of each dispensary, two hospitals have supervising nurses as well. Two employ no other graduate nurses. One employs seven graduate nurses in addition to the head nurse and supervisors. Two train students and postgraduate nurses in the dispensary. In no instance is home visiting carried on by the nurses.

Student Nursing—Training. One dispensary has no student nurses on duty. The other two employ eight, ten, and three, respectively. The length of the service in the same order is two and one months. All student nurses get experience in all departments of the dispensary in these instances. In no instance do student nurses do home visiting.

Social Service. Each dispensary has a social service department, the number of workers being respectively three, two, and six. In only one instance are these workers used only for dispensary cases. In only one instance are all new patients first seen by the social service department. However, each reports that social

histories are taken in all patients seen, and these histories are available to the attending physicians. Social histories have a permanent separate file in each clinic. Social service makes home visits in two instances.

All dispensaries use volunteers. They are in regular attendance, and their work in each instance is considered satisfactory.

Dietitian Service Two dispensaries have dietitians assigned them but only one for the dispensary alone. These dietitians see new patients only when they are referred by the clinicians, and if it is necessary, they are seen at proper regular intervals thereafter.

One dispensary supplies practical teaching in the preparation of diets to the dispensary patients.

GENERAL SUMMARY

Thirty-eight children's hospitals in the United States and Canada have been reviewed in previous reports. One of these hospitals was closed some time before the publication of the first report.

All of these hospitals are located in large cities with two exceptions, the Children's Hospital of Iowa City and the Children's University Hospital of Ann Arbor, Mich. These two hospitals are teaching institutions in connection with medical schools. Three of the hospitals are in Canada, thirty-eight (now thirty-seven) are in the United States. The distribution of the hospitals is not even, the northeastern part of the country having the largest number of these institutions. We find only nine west of the Mississippi River, and four of these are on the Pacific coast. The others are to be found one each in Kansas City, Iowa City, Denver, and Saint Louis. We might add the one in Winnipeg, Canada, to this group. The total number of beds in all hospitals is divided as follows: 500 to 600 bassinets, 1,500 to 1,600 cribs and 3,700 to 4,000 beds. Private rooms constitute only about 8 per cent. Wards predominate and about 60 per cent of the wards are divided into cubicles.

The institutions are usually located in fairly good neighborhoods. The cost per patient per day varies from \$1.87 to \$9.21.

As near as can be estimated from the White House Conference statistics, children's hospitals contain approximately one-fifteenth of the beds for children in the country. We may be sure that all beds reported as for children in children's hospitals are used for children. Quite the contrary is true in general hospitals, and the statistics derived from those sources are unreliable, so that it is altogether likely that the beds in children's hospitals constitute more nearly one-tenth than one-fifteenth of the hospital beds for children in the United States. We note with interest that only a very small proportion of the beds do not to exceed 8 per cent, are in private rooms. It should be borne in mind that private rooms are by no means always used for the care of private patients, for in most children's hospitals these private rooms are often used for the care of seriously ill children frequently these are charity cases. This fact brings out another very definite characteristic of the children's hospitals of this country, that they are essentially charity hospitals. We are pleased to report that in most of these children's hospitals medical teaching is done. Many of them are under the direct control of medical schools and many more are used for teaching purposes by medical schools. All physicians know that where such teaching facilities are provided in hospitals, the care of the patient is usually far above the general level of the care of patients in other hospitals of the same community. These facts in themselves speak very strongly for the excellence of the children's hospitals.

The hospitals derive their income from various sources. Many of them are city, state, or county institutions. Others are supported by local communities, and others,

largely by funds from endowment. No children's hospital so far as we are able to determine is at all near self supporting. As a rule, the income derived from patients is an exceedingly small proportion of the total income. We doubt if any children's hospital in the United States or Canada derives 5 per cent of its income from patients.

As far as the personnel of the hospitals is concerned, we should first consider the superintendents. The position of the superintendent in a modern hospital is one which requires excellent technical knowledge and much special training. Many of the superintendents of hospitals have grown up in hospital work, and the primary object of their early training has not necessarily been to fit them for that position. The time is fast approaching, however, when we must expect the superintendents of hospitals to be specially trained individuals and we will not choose them because they happen to have been previously associated with the hospital in some other capacity in which they showed good ability. One finds that among the group acting as superintendents of the children's hospitals a rather large number have been registered nurses. There is, of course, no reason why a registered nurse or a physician might not make a good hospital superintendent, but the fact that an individual is a physician or a registered nurse is no special recommendation for such a highly specialized position. We have no means of knowing whether the superintendents of these children's hospitals have had special training or not.

The attending staffs are adequate in practically every institution and are probably as good as can be obtained in the community since most of the hospitals are in connection with medical teaching centers.

As to the house staffs, there is a rather general recognition of the need for residents and the functions usually assigned to them. Many employ assistant residents as well, and all provide for internships. It should be said, however, that some of the children's hospitals have internes who take part time rotating services in general hospitals. Where this is true, the length of the service in the children's hospital is usually so short that the service to the hospital is practically of no value and the amount of knowledge gained by the interne is so small as to be only misleading. Internships for less than six months should be abolished.

As previously mentioned, the children's hospitals probably have been among the first to recognize and meet the responsibilities of all hospitals in their communities. They not only take care of a large number of charity cases, but they provide means for teaching physicians and medical students, many have courses for nursery maids and laymen to an extent that is not duplicated to our knowledge in other hospital groups. In other words, the teaching facilities in children's hospitals as viewed by our present standards are excellent. One of the essential functions of the children's hospitals is to disseminate knowledge regarding the child to all groups of the population. In general this work is well done.

The exact equipment and facilities of a hospital are difficult to determine from a questionnaire, but, according to the questionnaires which we have reviewed, it seems to us that these facilities are modern and adequate in most instances and that every means is taken to protect the children in these hospitals. The replies indicate that almost any type of case, if it is not too infectious in nature, may be brought into a children's hospital and there receive efficient care. Many of the children's hospitals either have their own contagious wards or have access to, and cooperate with, contagious hospitals.

In considering the nursing facilities offered by the children's hospitals in this country, we cannot formulate opinions from information concerning these hospitals alone. We must remember the somewhat frequent inadequacy of pediatric training for nurses in the general hospitals of this country and must also realize that many of these general hospitals send nurses to our children's hospitals for their pediatric

training. A comparatively small number of hospitals have the three year courses in pediatric training. Probably more of these courses are needed to provide special pediatric training for head nurses in wards in general hospitals or in the children's hospitals. We can only say that the number of nurses trained in the children's hospitals is probably too small to meet the demand for them and that this is not so much the fault of the children's hospitals as of the general hospitals which have not developed adequate facilities for the care of children and therefore make arrangements with children's hospitals whereby their nurses may receive only short and often inadequate training in case they expect to continue in children's nursing. The training that nurses receive in the children's hospitals of course varies greatly but on the whole it seems to be adequate in proportion to the amount of time spent. The hospital training in the hands of graduate nurses in all institutions seems to be open to a few criticisms. One great criticism however, is that most of the children's hospitals have not given sufficient attention to instruction in normal child psychology and behavior and comparatively few afford these nurses any experience in kindergarten or nursery school work.

As a whole, the physical equipment of the hospitals is good. Four fifths of them at least have physiotherapy departments. The diet kitchens seem to be adequate. Occupational therapy and schooling are available in about half of the hospitals. In a few instances there is considerable room for improvement in these departments as they can be important units in any hospital. It is rather surprising that more do not have them. Recreational facilities for convalescents are varied but again this is a weak department in many instances. X-ray facilities on the whole are good. The laboratory and pathologic departments apparently are fairly adequate. In many instances there is considerable room for improvement. It would seem to be relatively simple for many of these hospitals now lacking them to provide occupational therapy and schooling and it is to be hoped that they will do so.

The need for social service is generally recognized but there is some question as to the adequacy of the training of some of the persons who direct such departments. In most instances the work of the social service departments is very thoroughly done and volunteers are freely employed. The convalescent care for children however appears to be inadequate or at least can be considerably improved upon in nearly all of the hospitals.

Of the thirty-eight hospitals, thirty-six maintain dispensaries in direct connection with the hospital, and one of the hospitals as stated previously has closed. The dispensaries on the whole reflect the general excellence of the hospitals. The number treated in the dispensaries varies from less than 1,000 to 80,000 a year the fees charged from 10 cents to \$1.00. The dispensaries are almost without exception run in close connection with the hospitals and each has an interlocking staff in medicine, nursing and social service. While there is some variation in the type of work done, we may say that in general the facilities are excellent to insure efficient work. The dispensaries, as well as the hospitals, are used for teaching purposes, and in them physicians, medical students, nurses, and laymen receive instruction.

Academy News

Dr Maurice L. Blatt, of Chicago, has accepted the state chairmanship for Illinois

Dr Albert S. Root, of Raleigh, has accepted the state chairmanship for North Carolina.

Dr Edwin G. Schwarz, of Fort Worth, has accepted the state chairmanship for Texas

Dr D. Lesesne Smith, of Spartanburg, has accepted the state chairmanship for South Carolina

Dr Joseph I. Linde, of New Haven, has accepted the state chairmanship for Connecticut

Addendum

Hemophilus Pertussis Endoantigen (Krueger)

G. F. Munns, M.D., and C. A. Aldrich, M.D.

Since the publication of the article concerning Krueger's pertussis endoantigen,* the strength of the antigen has been increased to 10 mg of nitrogen per 100 c.c., representing approximately ten billion bacilli per cubic centimeter. The dosage as recommended for this preparation is as follows: Treatment, daily subcutaneous injections of from 0.5 to 2 c.c., the dose varying according to the therapeutic response of the patient. It is recommended that active treatment should be continued from ten to fifteen injections. For prevention in exposed cases or those liable to exposure, an initial dose of 1 c.c. is recommended followed every other day by 2 c.c. subcutaneously until six doses have been given.

Book Review

Traité de Médecine des Enfants. Published under the direction of P. NODÉCOURT and L. BABONNOIX. Editorial secretaries, J. Cathala and J. Hutinel, Masson et Cie. Libraires de l'Académie de Médecine. 120 Boulevard Saint-Germain, Paris. 1934. 5 volumes.

This five-volume work of 4762 printed pages is the first French system of pediatrics to be published since 1909, when V. Hutinel, father of one of the editorial secretaries of the present work published his *Les Maladies des Enfants* and Cruchet, his *La Pratique des Maladies des Enfants*. The last edition of Grancher and Comby's *Traité des Maladies des Enfants* is five years older. The appearance of the present *Traité*, therefore, is an important event in French pediatrics, and for pediatricians outside of France it affords an interesting opportunity to observe the development of the pediatric field in that country.

The two editorial directors MM. Nodécourt and Babonnoix, are well known by reputation to many Americans and represent the "school" of the late Victor Hutinel, as do the two editorial secretaries. Seventy-four collaborators have assisted in the preparation of various sections and the directors emphasize the fact that the list also includes followers of the other chief "school" of French pediatrics, that of Marfan. It is of some interest to note as reflecting the centralization of medicine in France that fifty-eight of these collaborators come from Paris, nine from Lyons and not more than one from any other one place. Two are from Switzerland. Some of the names such as Apert, Debré, Lereboullet, Lémé, Lhermitte, Pollicard Robin, Paul Rohmer, Tixier and others are well known to American pediatricians.

The first volume contains an interesting historical introduction, dealing almost exclusively with French pediatrics and there are sections on normal growth and disturbances of growth; on diseases of nutrition (including diabetes mellitus and insipidus 'arthritisme,' chronic articular rheumatism, and gout); diseases of the newborn on congenital malformations on deficiency diseases; on diseases of the endocrine glands; on "lymphatisme and lymphoscrophulose", on disorders caused by physical agents; on disturbances of heat regulation, and, finally on rapidly fatal hyperthermia after operation in young infants (the term "nouveau né" apparently applies to the first six months of life). Of these sections, that dealing with normal growth and development contains much valuable material, though it leaves out nearly all the anthropometric work of American students of the subject that on the deficiency diseases is excellent, diabetes mellitus is well and fully presented (apart from the omission of the names of the discoverers of insulin), that on the endocrine disorders contains much interesting material. The section on "arthritisme" (a diathesis alleged to include such diverse conditions as gout, obesity, diabetes, eczema, gallstones, kidney stones, asthma and chronic rheumatism) has no place in a modern treatise on pediatrics and reflects the familiar tenacity of tradition in French clinical medicine. To a lesser degree, the same remarks may be made of the section on "lymphatisme et lymphoscrophulose," although here the conception of diathesis is hedged about with many reservations the authors, in deed, concede that in most cases so called lymphatism is synonymous with scrofula (tuberculosis).

The second volume covers most of the specific infectious diseases, including typhoid, syphilis, tuberculosis, kala azar, typhus, dengue, Malta fever, relapsing fever, yellow fever, and others, diseases of the spleen and blood, including malignant lymphogranulomatosis (Hodgkin's disease). A final chapter is devoted to chronic cervical adenitis, serofula—illustrating again the persistence of the traditional conception of lymphatic enlargement in general as a pathologic entity in spite of the admitted etiologic diversity (tuberculosis, syphilis, lymphogranulomatosis, diseases of the blood, and malignant tumors are listed). This volume will be of particular reference value for its careful and detailed descriptions, from the pediatric aspect, of the "exotic" infectious diseases, such as dengue, typhus, Malta fever, yellow fever, etc., which are described in nearly all medical texts as they occur in adult life.

In Volume III, 131 pages are devoted to disorders of the heart and blood vessels. Descriptions of the congenital anomalies of the heart and vessels are in many instances disappointingly brief and inadequate. Coarctation of the aorta, for instance, is barely mentioned and, under arterial hypertension, is not suggested as a cause of high blood pressure in childhood. Almost nothing is said of electrocardiography. On the other hand, there are a number of instructive diagrams of the cardiac silhouette in various forms of cardiopathy, a good description of periarteritis nodosa (Kussmaul's disease), and some interesting notes on diseases and anomalies of the capillaries.

The larger part of this volume is given up to diseases of the respiratory tract. We note several good drawings of malformations and diseases of the larynx, and numerous excellent reproductions of radiograms, histopathologic preparations and temperature charts. The section on dilatations of the bronchi (including congenital cystic lung) is excellent, although, surprisingly, the names of Sicard and Forestier, who introduced iodized oil as a diagnostic method, are omitted. There is no section on foreign bodies. It is interesting to find the rôle of protein sensitization as an etiologic factor in asthma minimized. There are detailed descriptions of hydatid cysts of the lung, of actinomycosis, of tumors of the lung. Nearly 60 pages are devoted to pulmonary tuberculosis in childhood. The term "spleno pneumonia" (a separate section on this is to be found also under "pneumonia") is preferred by the French for what is elsewhere known as "perifocal reaction" and "epituberculous infiltration." The last 400 pages of this volume cover most of the digestive disorders of childhood. Paul Rohmer's chapters on intestinal obstructions, megacolon, and celiac diseases are excellent.

Volume IV includes descriptions of peritonitis, of diseases of the liver (including jaundice), of the kidney and urinary passages, of various forms of poisoning, of diseases of the bones and joints (including syphilis), on the skin, of the eye, and finally a portion on psychiatry. The section on the skin is particularly full and well illustrated.

The last volume is devoted mainly to diseases of the central nervous system and contains a large amount of most useful and instructive clinical material, upholding the high traditions of French neurology. This portion of the work will be most useful for purposes of reference to the general reader and to the specialist in neurology. It is, however, disappointing to find under poliomyelitis such incorrect statements about the experimental disease as that the rabbit is a susceptible animal, that the intraperitoneal route is apparently the best, that the virus is propagated via the lymphatic channels, and that the majority of the tissues and viscera are virulent—all these statements having been repeatedly disproved. There are good descriptions of acrodermia (called Selter's disease), Raynaud's disease, scleroderma,

etc. Tetany and spasmodophilia are included in this volume. The final 250 pages are given up to therapy and medication, and afford an interesting insight into the methods in popular use by French clinicians.

The index to the entire five volumes is at the end of Volume V and contains 43 pages. It is not entirely adequate. Proof reading has in many places been careless and the French typesetters have had their usual difficulties with English and American names, especially those beginning with "Mac" and "Me." F. A. McCollum will find his surname variously spelled "Mac Collum" and "Mac Callum." "Mellanby" is regularly spelled "Mellamby," etc. No consistent policy of bibliographic reference for the work as a whole has been followed. Some of the articles are fully documented. In others the names of authors are given only in parentheses in the text without citing title, journal or page, and in others no bibliography at all is offered.

The set is bound in boards with leatheroid backs. The paper is thin but opaque, smooth of good quality and permits excellent reproduction of the halftone and other illustrations. The type face is sharp and clear. The volumes are of convenient size (about seven by ten inches) for handling and, in general, the format is excellent.

This work containing as it does a large amount of highly valuable material, should find a place in all well-equipped medical libraries.

H. K. F.

Comments

AT THE meeting of the executive committee of the Academy in December, Dr Irvine McQuarrie, of Minneapolis, and Dr Grover F Powers, of New Haven, were added to the editorial board of the JOURNAL OF PEDIATRICS. The editorial board now consists of nine members including the editors. The editorial board is an active group which controls the general policies of the JOURNAL and is not merely a list of names for "window dressing." Manuscripts submitted to the JOURNAL must be approved for publication by at least two members of the editorial board.

THE appointment of Dr Martha Eliot as assistant chief of the Children's Bureau, which was announced in December, should give satisfaction to every one. Dr Eliot will have complete charge of the health activities of the Bureau. It would be difficult to find any one else more suited to or more capable of filling this position. Dr Eliot is unique in that she has not only the social interest in children which is necessary, but she has also earned general recognition in pediatrics and in the scientific side of medicine. A graduate of Radcliffe College and Johns Hopkins Medical School, her pediatric training was received in St. Louis, Boston, and New Haven. In 1927 she became assistant clinical professor of pediatrics at Yale University School of Medicine and in 1932 was promoted to associate clinical professor. For the last ten years she has been director of the Division of Child and Maternal Health of the United States Children's Bureau. We are proud that among her numerous memberships in medical societies she lists the Academy of Pediatrics and is chairman of the Committee on Child Health Relations. Her outstanding scientific contributions have been chiefly on the subject of rickets, and her numerous carefully planned and controlled studies are familiar to all of us.

We are confident that the appointment of such an outstanding and respected pediatrician as Dr Eliot will do much toward bringing the work of the Children's Bureau into a closer rapport with the medical profession as a whole than has existed in the past. We can be certain that the health activities of the Children's Bureau will be carefully planned from the medical standpoint, and she can be assured of our wholehearted cooperation.

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Original Communications

THE INTRAVENOUS ADMINISTRATION OF FAT

A PRACTICAL THERAPEUTIC PROCEDURE

L EMMETT HOLT JR., M.D., HERBERT C TIDWELL, PH D, AND
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BALTIMORE, MD

ALTHOUGH fat emulsions have been injected intravenously into animals by a number of different investigators, two obstacles have prevented the successful application of this procedure to man—the difficulty of obtaining an emulsion stable enough to resist sterilization and the danger of fat embolism. A few brave souls, to be sure, have given small amounts of fat by this route. Bondi and Neumann¹ made ultramicroscopic observations on the disappearance of injected fat particles from the blood stream, and Saxl and Donath² used this procedure as a clinical test for the activity of the reticuloendothelial system, it being supposed that fat particles injected into the circulating blood were removed by the phagocytic cells. During the Great War emulsified,³ and even unemulsified, camphorated oil⁴ was given intravenously, no dire consequences being recorded. It is only in recent years, however, that a technic has been developed whereby large quantities of emulsified fat could safely be administered. Credit for this achievement belongs to Yamakawa and his associates, who carried out a series of experimental and clinical studies⁵ in this field. They found that by using egg lecithin in sufficient quantities as an emulsifying agent it was possible to make emulsions that would resist sterilization by heat. By homogenization they produced emulsions in which practically none of the particles exceeded 2 μ in diameter, fine enough to pass without difficulty through

From the Department of Pediatrics John Hopkins University and the Harriet Lane Home Johns Hopkins Hospital.

Read at a meeting of the American Pediatric Society Asheville, N C, May 5, 1934. A discussion appears in the Transactions of the Society reprinted in Am. J Dis Child. 48: 526 1934.

The expenses of this investigation were defrayed in part by a grant from Mead Johnson and Company Evansville, Ind.

the lung capillaries* The practical difficulties which had stood in the way of intravenous fat therapy thus appeared to have been solved.

It is clear that intravenous fat administration, if feasible, will have important therapeutic applications As a parenteral food it should be of value in medical or surgical conditions demanding rest for the gastrointestinal tract, it offers particular advantages in infants with nutritional disorders who cannot digest adequate quantities of food given by mouth and whose fat reserves are readily depleted As a means of introducing calories, fat is more efficient than carbohydrate, and it may well be that it serves other more specific purposes as well Adequate proof of this last possibility has not been presented, but the observations of the Burrs⁷ on essential fatty acids, of Helmholtz⁸ on the bactericidal action of ketogenic diets, of Hanger⁹ and others on the effect of lipids in immune reactions, of Hansen¹⁰ on the influence of particular lipids in eczema, and of Harrop¹¹ on the importance of certain lipids in adrenal insufficiency are certainly suggestive

Various histologic and chemical studies have been made to ascertain the fate of fat introduced by vein As stated above, when the particles are too large, much of the fat is caught in the lungs, but when the emulsion is sufficiently fine, the bulk of the fat is removed from the circulation by the liver,¹² smaller portions being recoverable from the other organs and fat depots, at the height of lipemia fat may even appear in the urine Although some observers^{2 13} have found that fat particles accumulated in the phagocytic cells belonging to the reticuloendothelial system, there is equally definite evidence¹⁴ against this, even after moderately large doses of fat the organs have been found to present no histologic peculiarities, fat particles being present only in the parenchymal cells We ourselves, in collaboration with Dr G Lyman Duff, of the Department of Pathology, have made observations on six dogs given fat by vein, and we can confirm the finding that fat globules are visible only in the parenchymal cells unless the dose of fat has been extreme Possibly the discrepancies in the literature are due to the use of different preparations

The evidence in regard to the combustion of fat introduced by vein is not as complete as could be desired Observations in man are wanting † Murlin and Riche¹⁵ followed the respiratory quotient in two dogs after intravenous fat administration, finding changes comparable to those observed by Murlin and Lusk¹⁶ in dogs receiving fat by mouth On the other hand, Nomura¹⁷ working with rabbits was able to demonstrate the combustion of fat given by vein only when the animal's fat reserves had

*It is a curious fact that fat particles 4μ in diameter tend to be caught in the lung capillaries⁴ although red blood cells of twice this diameter pass through without difficulty

†Since this was written we have had the opportunity of seeing a paper by H. Gordon and S. Z. Levine (Am. J. Dis. Child in press) presenting calorimetric data on infants, which suggests that fat introduced by vein is promptly burned

been depleted by starvation. Baba²⁷ was able to demonstrate a fall in the respiratory quotient after the intravenous administration of fat in depancreatized rabbits or those treated with thyroxin.

Two clinical studies of parenteral feeding with intravenous fat have been published. Yamakawa's emulsion was developed for patients with peptic ulcer, and he and Nomura¹⁸ reported that several hundred patients had been so treated with satisfactory results, as much as 300 c.c. being administered at one time. Valledor, Casas, and Gomez del Rio¹⁹ reported a small series of infants with marasmus, in whom intravenous fat injections caused most encouraging results.

PERSONAL OBSERVATIONS

When our own studies were commenced, we were unfamiliar with the work of the Japanese investigators, but after trying various emulsifying agents* including soaps, bile salts and cholesterol, we reached the same conclusion as had Yamakawa—namely, that lecithin was the most satisfactory agent available. Moreover it seemed logical to use lecithin because of the work of Best and Hershey²⁰ which appeared at about that time, showing that lecithin and closely related substances would prevent the accumulation of fat in the liver of the depancreatized animal. We have prepared lecithin emulsions similar to that of Yamakawa, except in regard to the type of fat, which was varied, and we have also made some observations with the Yamakawa emulsion itself †

The Japanese emulsion contains 6.9 per cent total lipids suspended in distilled water, a trifle less than half of the lipid material is said to be egg lecithin, the remainder being a mixture of butter and cod liver oil. Our own emulsions contained from 7 to 7.5 per cent lipids. About one third of this material consisted of fresh commercial egg lecithin rectified with petroleum ether; the remainder consisted of various fats: olive oil, coconut oil, soy bean oil, butter or human body fat. We have avoided cod liver oil on theoretical grounds since there is evidence²¹ that it contains certain long chain highly unsaturated fatty acids that are not readily burned and tend to accumulate in the liver. Our emulsions were homogenized at 4,000 pounds' pressure and were then sterilized by autoclaving. Most of the fat particles were less than 2 μ in diameter, only a few being as large as 3 μ . The emulsions were rendered isotonic just before use by diluting with one tenth their volume of ten times physiologic saline.

After convincing ourselves that the injection of such preparations was attended by no risk, we proceeded to make a comparison of the various

*Much of this work was done by Dr. Warren M. Cox, Jr. who was associated with us at that time.

†Marketed by the pharmaceutical house of Sankyo in Tokio under the name "Yanol."

fats mentioned as regards the rate of disappearance from the blood stream after intravenous injection. The injections were given to normal infants following a twelve-hour fast, observations on the blood fat* were made just before the injection and at regular intervals thereafter. The quantity injected was arbitrarily chosen as 1 gm of total lipid per kilogram of body weight.

Our findings were altogether negative as far as the comparison of different fats was concerned. The type of lipemic curve varied to some extent in different individuals but was independent of the type of fat given. Typical curves are shown in Charts 1 and 2. This result might be interpreted as showing that the fats studied were equally well assimilated, a more probable explanation is that the rate of removal from

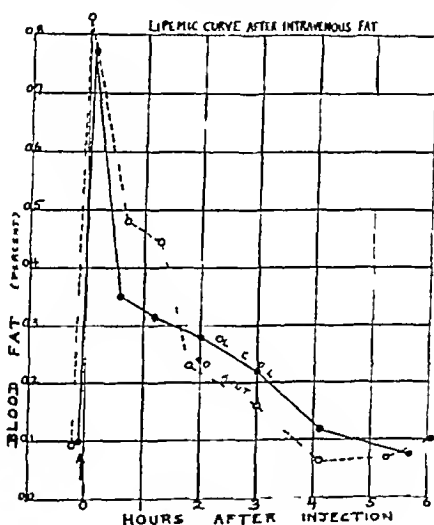


Chart 1—Baby C— Quantity 1 gm fat per kilogram Fasted before test.

the blood stream is determined by the lecithin coating of the particle. We studied one dog after an injection of mineral oil emulsified with lecithin and obtained a curve not appreciably different from that observed with emulsions of edible fats.

Although we had not succeeded in demonstrating that one fat was more readily assimilated than another when introduced intravenously, our therapeutic observations have been made almost exclusively with lecithin emulsions of olive oil. This seemed to give more stable emulsions than most of the fats we tried, moreover, our balance studies²³ had shown that this fat was exceptionally well absorbed from the intestine, and it

*The determinations of blood fat were made by Mr R. J. Myers and Miss E. G. Nichols using a modification of the micromethod of Gorter and Grendel.²² The extraction was made with ethyl ether from whole blood samples air dried on fat-free filter paper. This procedure extracts all neutral fat and free cholesterol traces of cholesterol esters but no phospholipid.

seemed possible that other tissues might handle it more readily. Mills²¹ found it particularly bland when introduced subcutaneously.

THERAPEUTIC RESULTS

Up to the present time we have used these emulsions for purposes of parenteral feeding in sixteen infants with severe nutritional disorders who received from 2 to 7 injections apiece on successive days; the dose was 1 gm. of lipid per kilogram in all but a few instances in which twice that quantity was given. Our experience has thus not been very extensive, and the present report must be regarded as a preliminary one. From our data it is not possible to form an unequivocal judgment as to the value of the treatment. A number of these cases were hopeless from the start—they were infants with tuberculous or pyogenic mening-

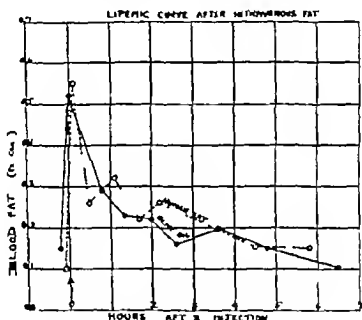


Chart 2.—Baby C—5 Quantity 1 gm. fat per kilogram Fasted before test.

itis, peritonitis or septicemia the fatal outcome which ensued can hardly be held against the treatment. In other instances even though recovery took place, it cannot be credited to the treatment, for other therapeutic measures—fluids transfusions—were simultaneously given. We shall present a few case histories, however, in which we gained the impression that the treatment had been responsible for improvement.

CASE 1—(H. L. H. No 83915) This was a full term baby birth weight unknown who weighed 6½ pounds (2905 gm.) when two weeks old. He was grossly underfed and lost weight steadily. The bowels alternated between constipation and starvation diarrhea. At no time was there any evidence of infection.

The patient was admitted to the hospital at the age of three and one half months weighing 4 pounds 12 ounces (2170 gm.) he was extremely emaciated and somewhat dehydrated. The dehydration was controlled by a single injection of intra-peritoneal saline. A diet was given providing 125 calories per kilogram which was gradually increased to 200 calories during the first week. Two transfusions were given during this period and were followed by mild reactions. Except for the

initial gain following the saline infusion, the patient's weight remained stationary during the first week and the first five days of the second week in the hospital, even though he was receiving 200 calories per kilogram during this latter period

Three fat injections were then given on successive days. After the second one the weight began to rise abruptly. A week later a second series of three injections on alternate days caused an accelerated gain of weight at that time. The patient continued to thrive, weighing 13 pounds, 4 ounces (6,135 gm) at the age of six and a half months.

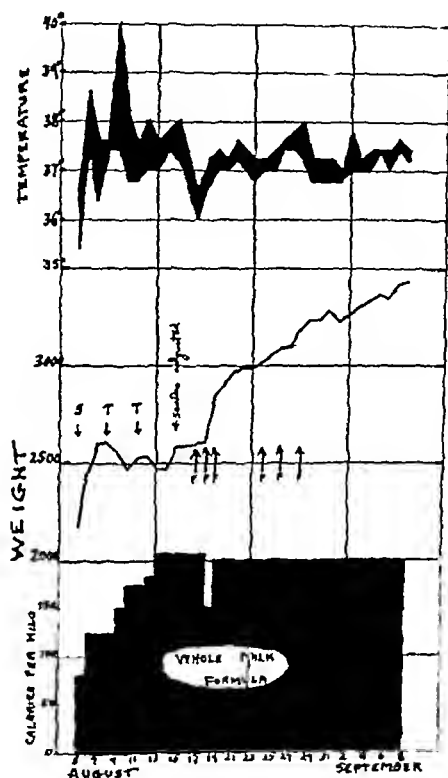


Chart 3—Case 1 (A S)

Although it seems likely that this patient would have started to gain sooner or later regardless of the fat injections, it is nevertheless striking that the gain in weight was so marked and coincided so closely with the administration of fat.

The following two cases were infants suffering from extreme malnutrition caused by diarrhea associated with infection of the upper respiratory tract.

CASE 2.—(H L H, No 85259, Unit No 49135) A twin, born on the obstetric service of the Johns Hopkins Hospital, progressed satisfactorily for one month but then began to refuse food, lost weight, and developed diarrhea. Pharyngitis and otitis media were noted subsequently. Subcutaneous saline was administered several times to overcome dehydration. The patient continued to lose weight and became

extremely emaciated, the features being pinched and the fat pads of the cheeks practically absent. Under the influence of daily fat injections and transfusions marked improvement took place, leading to eventual recovery.

It is worthy of comment here that saline alone (given prior to September 26) failed to check the loss of weight. With the introduction of intravenous fat (September 26 to 28) the weight increased, and there was improvement in the general appearance, despite a small peak in the temperature curve. The subsequent improvement (September 28

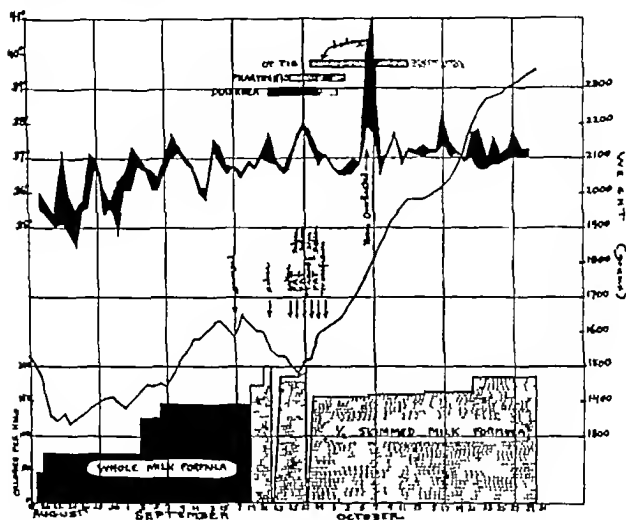


Chart 4.—Case 4 (M. L. H., Twin B)

onward) cannot be credited to the fat, for transfusions drainage of the middle ear, fall in temperature, and amelioration of the diarrhea doubtless contributed to this.

CASE 3—(H. L. H. No 84181) A full term infant, weighing $8\frac{1}{4}$ pounds at birth (3750 gm.) was admitted to the hospital at the age of two months having lost 2 pounds in weight. There was a history of a nasal discharge, almost continuous since birth, and refusal of food he had been given standard feedings. The patient was extremely malnourished and in addition to rhinitis there were rales in the chest and a low grade fever.

For three weeks the patient improved the bronchitis cleared up though some nasal discharge persisted after a single set back he seemed to be gaining weight. But on December 23 he developed a diarrhea with an exacerbation of the nasal discharge. Two days later there was evidence of dehydration, and parenteral saline was ad

ministered, the feedings were omitted for part of a day and then gradually increased. On December 27 the patient's condition was critical. The nasal discharge was extremely profuse, suggesting sinusitis, the diarrhea, which had abated with the reduction in food, reappeared promptly when this was increased to 70 calories per kilogram. It was clear that a further period of therapeutic starvation would not be tolerated, for malnutrition was extreme, the fat pads of the cheeks had gone entirely. It was decided to offer the patient 40 calories per kilogram by mouth and to supply 15 calories per kilogram each day in the form of intravenous fat. Within forty eight hours there was a marked change for the better in the child's appearance, the fat pads became palpable in the cheeks, the stools likewise were improved. The fat injections were kept up for six days, until the oral feeding had

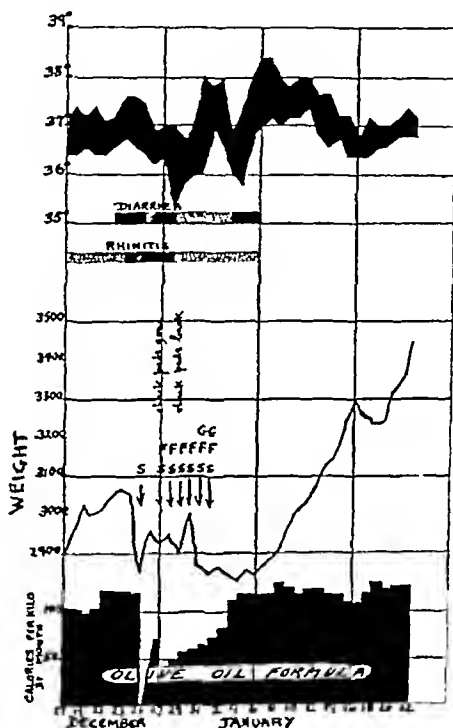


Chart 5—Case 3 (A. K.)

been increased to 70 calories per kilogram. Although the infection had not yet worn itself out, and the diarrhea returned for a time when the calories were increased to 100 per kilogram, a marked and permanent improvement followed this very shortly.

Although the intravenous fat supplied only about one-third of the basal requirements here, we gained the impression that it had exerted a favorable influence. It is possible of course that the improvement was due to an increased tolerance for food given by mouth. On the other hand, when one considers that the state of the bowels was still abnormal and that the amount of food given by mouth was still small, it is rather difficult to attribute the change in general appearance and the return of fat pads to the cheeks to oral food alone.

If we scrutinize our clinical material for possible ill-effects from the treatment, several points come up for discussion. On several occasions a slightly subnormal temperature was noted following the injection, such temperatures are by no means uncommon in the type of subject we were dealing with and the phenomenon was not constant enough to convince us that it was directly related to the treatment. On one occasion a transient glycosuria followed an injection, here again we doubt if the relation to the treatment was other than fortuitous. Four patients came to autopsy within forty-eight hours of a fat injection in all these instances there was adequate cause for the fatal termination and no evidence that the fat had played a part in it. The capillaries of the lungs and of the other organs showed no aggregations of fat, a fatty liver was, however, found in two of the four cases. The occurrence of fatty liver in patients with nutritional disturbances due to infection is by no means rare though an incidence of 50 per cent would hardly be expected. Some doubt exists as to the pathogenesis of this condition. Often there is no other evidence of liver pathology. The prevailing view²² regards the liver as suffering from a functional incapacity to utilize the fat which it removes from the blood; fat therefore accumulates in the liver cells. Probably there are instances in which the fat-consuming function of the liver is only slightly impaired in wasting conditions when the fat reserves are depleted and the blood fat diminished, such a liver might be able to handle a subnormal load without exhibiting fatty infiltration whereas if the normal load were supplied artificially fat accumulation would promptly take place. If this be the case one would expect that in clinical conditions likely to be associated with liver damage, the intravenous administration of fat might bring out an unusually high percentage of fatty livers.

Certainly there is no point in giving fat by vein to a patient whose liver is incapable of handling it; the administration of fat must be confined to those individuals whose liver performs this function normally. Up to the present time no clinical test has been developed to measure this function of the liver. We wish however, to call attention to the current report of Nachlas²³ who studied the lipemic curve after intravenous fat administration in experimentally produced hepatic lesions and found that this appeared to be an index of liver damage. It may be that this test will prove valuable in selecting cases in which benefit is to be expected from the intravenous administration of fat.

SUMMARY

- 1 It is possible to prepare fat emulsions that can safely be administered by vein
- 2 Our experience confirms that of others suggesting that these preparations are of value in parenteral feeding
- 3 The possible limitations of their use are discussed

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PERINATAL INFLUENCE IN RICKETS

I FETAL RICKETS

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ANTE-NATAL factors probably exert a considerable influence toward the rachitic tendency in the infant and may in some instances be of such magnitude as to cause the development of rickets in the fetus in utero. Maternal health and deficiency of essential elements in the diet during gestation, frequency of pregnancies, and inadequate exposure to sunlight are among the antenatal factors which appear to be important.

1 *Maternal Health and the Diet During Gestation*

It is known primarily from experimental evidence, that parental nutrition is capable of exerting a definite influence on the occurrence of rickets in the offspring. Grant and Goettsch¹ found that in rats the diet of the mother was an important factor in increasing or decreasing the resistance of the young rats to the effects of diets that had been depleted of antirachitic factor alone. Grant² was also able to demonstrate that a lack of both vitamin D and minerals (calcium and phosphorus) in the diet of the mother rat produced rickets in the offspring which became manifest earlier and progressed faster than if the diet had been poor in the vitamin only. Somewhat similar findings were noted by Byfield and Daniels.³ Toverud and Toverud⁴ made a further contribution to this subject when they were able to create in the puppies of gravid dogs fed on a diet low in both minerals and the antirachitic factor an early and severe rickets far more pronounced than in puppies from mothers on an adequate diet.

The significance of early craniotabes and so-called 'congenital osteoporosis' of the skull in relation to their much disputed association with rickets cannot be reviewed in detail but some investigations carried out by Abels and Karplus⁵ appear pertinent. These authors state that 'soft skulls' (thin, soft, easily compressible bones with wide-open sutures and large fontanels) in newborn infants rest upon nutritional defects of the mother. They feel that 'soft skulls' represent prerachitic changes and find that these young infants manifest an increased tendency to develop rickets later. Recent confirmation of this comes from Toverud⁶ who not only maintains that newborn infants with soft skulls are born almost exclusively of women with a distinct deficiency in either diet or health but also that 'hard skulls' in contradistinction are born largely of mothers whose diet and health has been adequate and normal.

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The Toveruds⁴ and others⁷ have found that where maternal health and diet have been sufficiently poor, the infants show fringing, poorly calcified epiphyses although Hess and Weinstock,⁸ who previously encountered such changes, feel that they are equivocal and not necessarily pathognomonic of rickets. The latter authors, after the roentgenologic examination of the epiphyses of 250 newborn infants concluded that "although the incidence and severity of rickets may be influenced by improving prenatal nutrition, the disease is mainly of postnatal origin." While this statement is undoubtedly true, roentgenologic changes occur as a relatively late manifestation of rickets, and early roentgenologic examination may fail to disclose the disease.

B Frequency of Pregnancy

As far as could be ascertained, frequency of pregnancy in the mother has not been given due consideration as a possible antenatal factor in the development of rickets in the infant. That this factor should have been neglected is surprising when one realizes the close correlation between osteomalacia and rickets and the effects that the advent of pregnancy brings in the former disorder. Recent work, particularly in China⁹⁻¹⁰ and India,¹¹⁻¹² indicates that these two disorders are due to a single cause, i.e., vitamin D deficiency. Both show the same relation to season and sunlight, the same response to cod liver oil and similar chemical changes in the blood of patients. Histologically the bones of osteomalacia give the appearance of rickets as it might be expected to appear if involving the adult bone. Miles and Feng¹³ have shown that osteomalacia is frequently precipitated by the gravid state and becomes more acute during the later months of pregnancy. Not infrequently an initial appearance is delayed until parity has become multiple, and with each subsequent pregnancy the disease becomes more severe. According to Hess,¹⁴ one observer has gone so far as to state that in the course of any normal pregnancy the bones undergo mild osteomalacic changes of subroentgenologic character, due to an abnormal intensification of the physiologic drain of inorganic salts, which takes place during gestation. This work, adds Hess, has never been refuted or confirmed.

Hess and Matzner¹⁵ found that while the inorganic phosphorus of the blood of pregnant women may be approximately normal, the calcium is reduced at term. Toverud and Toverud⁴ have demonstrated that women (on an average Norwegian diet) often show a negative calcium and phosphorus balance during gestation and, less frequently, during lactation. They likewise have shown that the calcium content of breast milk may become subnormal. Even in the presence of an adequate diet during pregnancy, Jundell and Magnusson¹⁶ believe that the administration of cod liver oil to the mother raises the inorganic phosphorus content of umbilical cord blood. Working on rats, Grant and Goettsch¹ determined that under ordinary circumstances

rickets does not develop readily in the offspring of well nourished rats when a partial lack of the antirachitic vitamin is the only deficiency in the diet. When these same rats on the same diet are forced into repeated pregnancies in the absence of sunshine the later litters exhibit a strong tendency to early and severe rickets. A clinical example of the effect of repeated pregnancies is well illustrated in a case of severe rickets reported by Jungwirth¹⁷. In this instance the mother had undergone eight pregnancies in a short time, and while the first five sibilings were quite normal, the last three all had rickets. Each case was more severe than its predecessor. A case recently studied in this clinic that will be reported in detail elsewhere represents another example. The mother had five children in nine years. Three of them showed no evidences suggestive of rickets, but the two younger children both had florid rickets, the last born showing extensive involvement at the age of two months.

C Effect of Sunshine on Mother and Fetus

That insufficient exposure of the mother to the actinic rays of the sun may play a not inconsiderable part in the causation of early rickets is evidenced by an extensive survey conducted by Hutchison and Sha¹⁸ in India. They learned that 25 per cent of the infants from well-to-do mothers who practiced "purdah"^{*} had definite signs of rickets, whereas only 5 per cent of the children from the lower caste Hindus had evidence of the disease. The mothers of this latter group do not observe "purdah" and get an abundance of sunshine. Further enlightenment is to be had from the studies of Grant which have already been discussed.

FETAL OR CONGENITAL RICKETS

Antenatal factors, while undoubtedly capable of exerting an influence toward a rachitic tendency in the infant are rarely of sufficient magnitude to create rickets in utero. The occurrence of the disorder in the unborn child was for many years not countenanced by many workers, who based their conclusions largely on the investigations of Schmorl¹⁹. He concluded, because of failure to find histologic evidence of rickets in an examination of over one hundred full term and prematurely born infants coming to necropsy, that fetal rickets did not exist. The series of cases would appear rather small to justify such a conclusion.

Occasional reports of congenital rickets have appeared. Most of these reports have lacked the important essential of histologic corroboration. It was not until Maxwell began his investigations in China that fetal rickets was definitely established as an entity. Several years ago he and Miles⁹ called attention to the incidence of

* A form of religious seclusion practiced by high caste Hindu and Mohammedan women.

osteomalacia in certain districts of China and showed that the diets of the mothers afflicted with this disease were deficient in calcium, phosphorus, and vitamin D. In 1930 Maxwell and Turnbull²⁰ presented evidence suggestive of the existence of fetal rickets in infants born of osteomalacic mothers. Two cases were cited in one of these the evidence was afforded only by roentgenogram, while in the other the badly preserved condition of the bones detracted to some extent from the value of the material presented.

In 1932 Maxwell and his coworkers¹⁰ established beyond any doubt that rickets does occur in utero. A detailed report was presented of a Chinese woman aged thirty-eight years, who had been on a starvation diet (consisting of two daily meals and containing no meat or animal fat) for three years and had suffered from the pains of osteomalacia for two years. At the time of delivery she had a hypocalcemia (7.38 milligrams per cent), and the infant weighing 2,835 gm., showed a marked rosary and Harrison's grooves. Radiograms of the infant disclosed rachitic-like changes of the long bones that were later verified by histologic examination.

As Turnbull points out, there is no histologic distinction between osteomalacia and rickets, but we do not definitely know that the two conditions are identical. Thus, "if osteomalacia differs causally from rickets, then these infants are the osteomalacic offspring of osteomalacic mothers."

REPORT OF AN ADDITIONAL CASE OF FETAL RICKETS

While osteomalacia is encountered frequently in China and India and is common in certain parts of Central Europe, it is seldom recognized in America. As a consequence one would hardly expect to see congenital rickets in this country. Nevertheless an additional case, the fourth to be reported and the second proved case, has been encountered in Massachusetts.

Baby C, a white female infant two days of age, was admitted to the hospital because of bleeding from the nose and mouth.

The mother, thirty-two years old, had been in an extremely poor nutritional state throughout pregnancy. She had been vomiting severely for weeks and had been able to retain little food. During the latter months of pregnancy she suffered from hypertension and at the time of delivery had albuminuria and marked secondary anemia.

The baby was delivered at full term by podalic version and breech extraction. The immediate postnatal condition of the infant was good, and the birth weight was said to have been about 7 pounds and 8 ounces. Approximately eight hours after birth, however, spontaneous bleeding from the nose and mouth occurred. On the following day an attending physician administered 25 c.c. of whole blood intramuscularly without effect. The condition of the infant became progressively worse, repeated hematemesis took place, respiratory irregularity developed, and death occurred on the second day of life.

Radiograms of the costochondral junctions disclosed a marked flare and irregular metaphyseal cupping.

Abstract of Autopsy Protocol

Necropsy was performed four hours postmortem. The body was that of a well nourished and developed white female infant whose general appearance was not unusual except for a marked rosary of rachitic type. There was gross hemorrhage into the scalp alimentary tract, and into the retroperitoneal tissue of the right iliac



Fig. 1.—Photograph of split sections of three ribs showing the costochondral junctions. Note the irregularity of the metaphyseal lines, overproduction of cartilage, and distortion and swelling of the costochondral junctions.

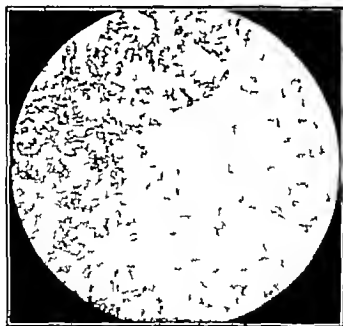


Fig. 2.—Photomicrograph of section of rib showing an area in the region of the metaphyseal-epiphyseal junction. Note overgrowth and disorganization of columns of cartilage, evidences of lack of normal cartilage, invasion and bone formation, excess osteoid tissue, and irregularity of metaphyseal line. (Hematoxylin and eosin, X80.)

region. In addition, there were petechial hemorrhages in the thymus, heart, lungs and bladder, with congestion of the spleen, liver, kidneys, adrenals, and brain.

The most interesting findings were those in the bones. Gross inspection revealed a marked thickening of the costochondral junctions (Fig. 1). The primary zone of ossification was slightly irregular and moderately thickened. The periosteum and perichondrium were not remarkable, and there was no subperiosteal hemorrhage. A

striking feature was the marked pallor and density of the trabecular bone, particularly in the vertebrae

Eight sections of bone were made, four of costochondral junction and four of vertebrae. Microscopic examination of the latter showed well developed trabecular bone containing the usual islands of cartilage. The interstices were well filled with active hematopoietic cells, and there was a narrow, regular osteochondral junction. Histologic sections of the costochondral junction, however, showed a marked deviation from normal, principally due to a much thickened, widened, and very cellular preparatory zone of cartilage (Fig 2). The junction between bone and cartilage was irregularly convex toward the diaphysis. The cartilage showed no evidence of preliminary calcification and had been irregularly invaded by both marrow and perichondrial vessels. There were small amounts of osteoid tissue. The bone spicules were thin but numerous and calcified. Many giant cells were seen on the periosteal surface of the cortical bone on the inner aspect of the ribs. These were less numerous on the surface of the spicules. Osteoblasts were abundant, and there was a moderate amount of active marrow.

Anatomical diagnosis: hemorrhagic disease of newborn, fetal rickets.

SUMMARY

A review of the literature on prenatal influence in rickets indicates that maternal health and diet are outstanding etiologic factors and that frequent pregnancies and lack of exposure to sunshine may be contributory factors which exert an influence on the development of rickets in the very young infant.

A case of fetal rickets established by roentgenograms of the bones and confirmed by histologic examination is reported. The rachitic process in the infant was apparently due to severe malnutrition in the mother.

I am indebted to Dr Sidney Farber, of the Department of Pathology of the Harvard Medical School, for the study of the pathologic material.

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PRENATAL INFLUENCE IN RICKETS

II EARLY POSTNATAL RICKETS AND FLORID RICKETS WITH MULTIPLE FRACTURES

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IN A previous paper attention was directed to antenatal influence in rickets and to the occurrence of fetal rickets. Some of the important prenatal factors were discussed and a case of fetal rickets was reported¹

The purpose of this study is to ascertain the effect of maternal influence on the development of certain other forms of rickets in the infant. The study is based upon a survey of 400 cases of active rickets

A EARLY POSTNATAL RICKETS IN THE INFANT BORN AT TERM

Investigators have rather uniformly agreed that rickets is a rarity under three months of age and yet the literature yields little as to the actual incidence in this age group. Hess² states that rickets begins about the third month and ends about the eighteenth month. Holt and McIntosh³ mention the period from the fourth to the eighteenth month and go on to say that the disease is rare before the third month and after the second year. Schmorl⁴ in 1909 conducted a pathologic study on 365 cases of rickets examined at autopsy and found histologic evidence of the disease in twenty infants under three months of age an incidence of 5.5 per cent. Four of the patients were two months old and the others were all between two and three months old. It is well known that premature infants and twins are susceptible to early and severe rickets. Ylppo⁵ has observed rickets in a premature infant at the age of six weeks. The youngest patient with rickets described in this country was an infant thirty four days old, reported by Dnnham⁶ and while this baby was allegedly born prematurely its birth weight was 3,260 gm.

Rickets in the Infant Born at Term—In an attempt to determine the actual incidence of early rickets and to investigate possible etiologic factors of significance 400 cases of rickets seen in this clinic over a period of the past nine years have been reviewed. All of these were in an active phase of the disease, and in each instance clinical diagnosis was corroborated by roentgenographic examination and chemi-

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cal analysis of the blood. Only patients with abnormally low phosphorus have been included in this survey.

In this series of 400 it was found that thirty-two cases, or 8 per cent, were aged three months or younger. Of these, the youngest was a full-term infant of thirty-five days. Fourteen of the thirty-two were under two months of age, and eighteen infants were from two to three months old.

When one considers the generally accepted rarity of rickets in the first three months of life, it is surprising to find that 8 per cent of the cases of rickets developed in this age group. Exactly half of the infants were the result either of premature birth or of twin pregnancy. The other sixteen infants were all born at full term.

Thus among 400 cases of rickets 4 per cent (sixteen cases) occurred in full-term infants under three months of age. Among these, 1.75 per cent were less than two months old, and 2.25 per cent were in their second or third month of life. None of the sixteen had a birth weight of less than 6 pounds and 12 ounces, which is well above the figure arbitrarily accepted as one of the indices of prematurity. The average weight at birth was 7 pounds.

Comment—With only three exceptions this group of full-term infants presented on admission an excellent state of nutrition and had shown consistent gains in weight since birth. Most of them appeared healthy and hospitalization was usually requested because of mild respiratory infection or convulsions from an associated tetany. The association of tetany with rickets in these very young infants is worthy of note. A recent analysis by Guild⁷ of 293 cases of tetany from the Harriet Lane Home disclosed an incidence of 7½ per cent in patients under three months. Since infantile tetany almost always develops on the basis of a previous rickets, the close parallelism between this figure and the 8 per cent incidence of rickets found in this series for the same age group is of interest. The youngest case of tetany in the recent literature was reported in a nine day-old infant by Small.⁸

It is known that "roentgenologic rickets" indicates a fairly advanced stage of the disease, for in 1928 Wimberger⁹ demonstrated that the interval between the first histologic rachitic change and the first radiographic change is "certainly as long as several weeks." When one recalls that almost half of this full-term group showed roentgenologic evidence of the disease prior to the second month, it at once becomes evident that in them the disorder must have had its incipency in the very early weeks after birth.

Turning to an analysis of possible contributory factors to the development of such an early rickets it is seen that prenatal influence may be of importance (Table I). An investigation of maternal health and diet during pregnancy was not quite as satisfactory as might be

TABLE I
CASE ANALYSIS OF ETIOLOGIC FACTORS IN FULL-TERM INFANTS WITH ACTIVE RICKETS UNDER THREE MONTHS

CASE	ANTENATAL FACTORS				POSTNATAL FACTORS				
	MATERNAL DIET	MATERNAL HEALTH	YEARS MARRIED	NUMBER OF CHILDREN	SEX	NATIONALITY	FEEDING	COD LIVER OIL	MONTH
1	Unknown	Poor	3	0	F	Irish	Breast	Adequate	August
2	Deficient	Poor	3	1	F	Irish	Breast	None	October
3	Unknown	Unknown	Unknown	Unknown	M	American	Artificial	None	February
4	Good	Good	7	6	F	Scottish	Breast	None	September
5	Unknown	Unknown	Unknown	Unknown	M	American	Breast	None	November
6	Unknown	Unknown	9	6	M	Irish	Breast	None	March
7	Deficient	Unknown	17	3	M	Italian	Artificial	Inadequate	September
8	Unknown	Unknown	6	9	F	German	Breast	None	April
9	Unknown	Unknown	Unknown	5	M	Scottish	Breast	None	January
10	Unknown	Unknown	13	Unknown	F	Scottish	Artificial	None	March
11	Unknown	Unknown	10	6	F	American	Breast	None	October
12	Good	Good	10	9	M	Irish	Breast	None	June
13	Unknown	Poor	4	2	F	Italian	Breast	Adequate	January
14	Unknown	Unknown	Unknown	Unknown	M	Irish	Artificial	None	December
15	Unknown	Unknown	8	3	F	American	Breast	None	February
16	Deficient	Poor	2.5	2	F	German	Breast	None	May

desired because relevant data could be accumulated in only seven of the sixteen cases. In these however, the results were striking. Only two of the mothers had been healthy and had received an adequate diet. Five of the women had a rachitogenic diet, poor health, or both. Their diets consisted largely of fruits and vegetables with no meat, no milk, and no eggs. Impairment of health was so extreme that confinement indoors had resulted, in at least three cases there was practically no exposure to sunlight during the latter months of pregnancy. Frequent pregnancies were a prominent feature in the maternal background. Seventy-five per cent of these mothers had five or more children in nearly as many years. They were women who nursed their young, usually for a prolonged period. Thus it may be seen that in almost every case there was at least one, and often a combination of maternal factors, which might influence the growth and development of the infant. Each of these factors, poor health, deficient diets, frequent pregnancies, absence of exposure to sunshine and prolonged lactation, may exert an influence on the infant to impair bodily nutrition, alter metabolism, and particularly to create a depletion of maternal and fetal calcium and phosphorus.

Consideration of postnatal factors yields little information with respect to the causation of early rickets. Nationality, sex, season, and infection were not contributory. The only points seemingly worthy of note were moderately rapid weight gains and an absence of cod liver oil from most of the infant dietaries. An actively growing infant, who is not given cod liver oil or a substitute, will usually show some degree of rachitic change eventually unless there is frequent exposure to sunshine. It is to be recalled, however, that 75 per cent (twelve cases) of the babies under consideration were breast fed. In view of the relative infrequency of rickets in the breast-fed infant, it seems likely that the development of early postnatal rickets was dependent largely upon nutritional defects in the mother. In the light of present knowledge the mechanism of this relationship cannot be definitely stated although it may well be much the same as that which probably obtains in the premature infant. The latter has a deficiency of stored calcium and phosphorus, due presumably to an immature maturation incident to an early termination of intrauterine life. The full-term infant born of a mother impoverished nutritionally also has a lack of stored calcium and phosphorus, but this occurs as a result of impaired metabolism on the part of the mother. Several years ago Hess and Matzner¹⁰ decided that the percentage of inorganic phosphorus and calcium in the circulating blood of the newborn bore no relationship to the occurrence of rickets during the first year, but some recent work by Toverud and Toverud¹¹ may be of significance. Working on young puppies born of dogs placed on rachitogenic diets, they were able to produce an early and extensive rickets far more

pronounced than in control puppies born from nutritionally sound mothers. While these puppies at birth revealed no histologic or roentgenologic evidence of rickets, a chemical analysis of the bones disclosed a distinct lowering in the calcium and phosphorus content throughout the skeleton.

In the series of cases reported the nutritional defects of the maternal organism were not of sufficient magnitude to produce an actual rickets in the infant prior to birth. Instead a moderately defective nutritional state possibly induced a "congenital tendency" which was elaborated primarily through an impaired mineralization of fetal bone. Changes incident to the great growth stimulus cause, following birth, an increased depletion of calcium and phosphorus and the "congenital tendency" becomes the actual disease.

B SEVERE INFANTILE RICKETS WITH MULTIPLE FRACTURES

Cases of rickets are encountered which manifest an extremely severe form of the disease with marked osteoporosis that results in spontaneous multiple fractures. Excluding such factors as race and possibly an increased disposition to rickets sometimes in evidence throughout certain families, one is usually at a loss to explain these types of the disease. A review of the literature shows a surprising dearth of material on the subject. The association of fractures with rachitic bone changes has been reported in this country by Dunham,⁸ Hess,² and Park and Howland.¹² The last named authors describe a series of negro children with advanced rickets and severe thoracic deformities, some of these patients showed multiple fractures of the extremities. Cases have been recorded elsewhere by Lereboullet and Chabun,¹³ Steiner,¹⁴ and Jungwirth.¹⁵ Apparently as age increases the incidence of fractures becomes higher. In the late rickets (*rachitis tarda*) of childhood and the osteomalacia of puberty and pregnancy fractures become very common. Hutchinson and Stapleton¹⁶ have reported a number of cases of this type from India. The only case of a rachitic patient with fractures under three months of age that could be found was Dunham's case of rickets in an infant thirty four days old. This baby had multiple fractures of the ribs.

CASE REPORT

A case of flagrant rickets that showed multiple fractures at the age of two months was recently studied in this clinic. The case is thought to be sufficiently unusual to warrant a report in some detail because of the extreme rarity of multiple fractures at this age and because of the possible influence of maternal factors on the development of the disease.

G M, a four month old female infant from a poor Italian family, entered the hospital on Sept 12, 1933, with a complaint of "failure to gain." The mother was twenty five years old, she had been married for nine years, and this was the fifth child. Her health had been poor for several years, and with the onset of this pregnancy it became much worse. There was a constant nausea present, throughout pregnancy she ate little except cooked vegetables, occasional small amounts of raw fruits (oranges and apples) and soup. Meats, milk, and eggs were entirely excluded from this self imposed diet. A vaginal discharge had been present for some months and during the height of pregnancy she developed severe pains in her legs and joints diagnosed as "gonorrheal arthritis." These became of such severity that during the latter months of confinement she was unable to descend stairs and was forced to remain in a room that received little sunlight. Weakness was an outstanding feature. Severe dental caries developed. Following a full term, difficult delivery, there was considerable spontaneous improvement of her pain, and subsequent ultraviolet irradiation created a prompt remission. The family history was of further interest. Three of the four siblings were in good health, but the youngest, aged two years, showed evidence of an advanced rickets with a large square head, prominent frontal bosses, rachitic rosary, extensive bowing of the legs, and epiphyseal enlargement.

The patient weighed 6 pounds and 4 ounces at birth, and her immediate post natal condition was good. She was placed on a modification containing dextrimaltose, milk, and water. This was taken with avidity, and, while the infant seemed in good condition, she was unable to gain consistently. Orange juice was begun at one month and administered thereafter in adequate amounts. During the ensuing weeks the infant continued in uneventful fashion until she was two months old. At this time the mother detected a swelling of the "front of the left shin bone." This was only slightly tender, seemed quite hard, and in no way curtailed the baby's activities. A few days later there occurred a single generalized convulsion. Cod liver oil was then begun in daily teaspoon amounts but after one month it was discontinued because of occasional attacks of diarrhea. The baby still showed no tendency to gain, and finally at the age of four months she was brought to the hospital for investigation.

On admission, examination disclosed an underdeveloped and markedly undernourished, hypertonic female infant who weighed 7 pounds and 5 ounces. She appeared chronically ill, color was an ashen pallor, and skin turgor was poor. The head was of square configuration with prominence of supraorbital bosses. There was no demonstrable craniotabes. A rosary of rachitic type was present, and a beginning Harrison's groove was detectable. The abdomen was quite protuberant and the splenic edge could be palpated 2 cm below the costal margin. Epiphyseal enlargement was not evident, but over the anterolateral aspect of the left tibia a rather diffuse swelling could readily be seen. This was hard in consistency, seemed to be contiguous with the bone, and was not tender to manipulation. There was frequent spontaneous movement of all extremities without apparent discomfort.

An anemia of hypochromic type was found, serum calcium content was 7.7 mg per 100 cc,* and the inorganic phosphorus was 4.5 mg per cent†. A plasma phosphatase content of 13 units per cubic centimeter‡ was indicative of advanced active rickets. Other data, including serum protein, nonprotein nitrogen, and renal function tests, were within normal limits. Mantonx tuberculin tests, run up

*Calcium determination by method of Fiske—normal range during first year from 9 to 12mg per cent

†Phosphorus determination by method of Fiske and Subbarow—normal range during first year from 4.5 to 5.5 mg per cent.

‡Phosphatase determination by method of Kay—normal range for infants under one year from 0.10 to 0.27 units per cubic centimeter

to 100 mg of old tuberculin, produced no reaction. The Wassermann Hinton, and Kahn reactions on both parents and baby were negative.

Roentgenograms (Sept. 13, 1933) showed multiple fractures including the left clavicle the seventh left rib anteriorly, the left radius, left ulna and the right radius. There were also two fractures of the left tibia and two of the left fibula. There were all surrounded by a moderate amount of callus formation. There was an extreme degree of generalized osteoporosis and the metaphyseal margins were irregular and defectively calcified (Fig 1)

The infant was immediately placed on a vigorous antirachitic regimen consisting of liberal amounts of a halibut liver oil preparation fortified with viosterol. Ultra violet irradiation was given. Reexamination of the long bones two weeks after entry (Sept 26 1933) showed definite improvement characterized by an increase in the amount and density of the callus around the fractures. Likewise the osteoid at



Fig 1.

Fig 2.

Fig. 1—A film of the lower extremities taken Sept. 13 1933. Note the generalized osteoporosis, the irregular metaphyseal margins and multiple fractures. There are two fractures of the left tibia and two of the left fibula.

Fig. 2—Roentgenogram at time of discharge, Nov. 14 1933. This illustrates complete healing of the fractures in good position with no remaining evidence of previous existence. Calcification has become almost normal, but slight rachitic changes are still extant.

the ends of the long bones showed increased calcification. Serum calcium at this time had risen to 12.4 mg per cent and phosphorus to 5.9 mg. Another film taken two weeks later (Oct. 11, 1933) disclosed well calcified metaphyses and all of the fractures almost united. Six weeks after admission the fractures were well healed, and the only evidence of their previous existence was a small amount of unresolved callus in the left tibia. Upon discharge two months after entry (Nov. 16 1933) the radiograph demonstrated complete effacement of all fracture lines although there were some slight rachitic changes still present (Fig 2). Serum calcium was then 10 mg per 100 c.c., and phosphorus, 5.7. A plasma phosphatase of 0.51 units

per cubic centimeter was further evidence that healing was as yet not complete. Throughout her stay there was marked general improvement and a weight gain of almost five pounds in two months.

That osteomalacia was present in the mother during the latter months of her pregnancy seems probable. A rachitogenic diet, frequent pregnancies, poor health, and an insufficient exposure to sunshine are all etiologic factors to the development of this disorder. The disease is further suggested by the extreme weakness and severe joint pain, which are outstanding symptoms of osteomalacia. At the time she was seen, however, this diagnosis could not be confirmed. A radiograph of her extremities taken six months postpartum (Nov 16, 1933) showed nothing of note although this is not surprising in view of the fact that her diet since delivery had been normal. She had also received over a month of intensive ultraviolet light therapy, which would contribute to further healing. A request for calcium and phosphorus determination on the mother was refused.

This case, in several respects, resembles the one reported by Dunham. The mother of that baby had undergone seven pregnancies, had been exposed to very little sunlight, and her diet had been very deficient. During the latter months of pregnancy weakness and pain in the legs developed. X-rays disclosed considerable rarefaction of the bones, it was likely that she had osteomalacia.

A SURVEY OF 400 CASES OF ACTIVE RICKETS WITH AN ANALYSIS OF CASES WITH FRACTURES

Of the four hundred cases of ^{rickets} surveyed by the author, fractures occurred in fourteen instances, an incidence of 3.5 per cent. Nine of the patients who developed fractures were full-term infants and the remainder were either premature infants or twins.

The age incidence in this group closely followed that usually seen in rickets, with an average range of from six to fifteen months. The youngest was two months old, and the oldest, twenty six months. Only two cases were found in infants under three months of age.

The patients with severe rickets associated with fractures entered the hospital with a chief complaint of "failure to gain" or "cough." Almost without exception they presented extreme degrees of malnutrition and underdevelopment. Severe respiratory infections were frequent, and the mortality in the group was 29 per cent, death occurring from bronchopneumonia.

COMMENT

The etiologic factor in the causation of severe rickets with fractures cannot be definitely stated. Postnatal factors did not seem to be outstanding (Table II). Sex, season, and nationality were hardly worthy of connotation. Five of the fourteen infants were breast fed,

TABLE II
CASE ANALYSIS OF ETIOLOGIC FACTORS IN INFANTS WITH FRACTURES

CASE	ANTENATAL FACTORS				POSTNATAL FACTORS				
	MATERNAL DIET	MATERNAL HEALTH	YEARS MARRIED	NUMBER OF CHILDREN	SEX	NATIONALITY	FEEDING	COO LIVER OIL	MONTH
1	Unknown	Unknown	4	2	M	Irish	Breast	None	December
2	Unknown	Poor	11	7	M	Italian	Artificial	Adequate	October
3	Deficient	Poor	5	3	F	American	Artificial	Adequate	February
4	Unknown	Unknown	8	6	M	Greek	Breast	Inadequate	April
5	Unknown	Poor	1	1	F	American	Artificial	None	July
6	Good	Good	1	2	F	Irish	Artificial	None	February
7	Deficient	Poor	0	3	F	Italian	Artificial	Inadequate	September
8	Unknown	Unknown	6	5	M	Italian	Breast	Adequate	August
9	Unknown	Poor	3	1	F	Scotch	Artificial	None	July
10	Unknown	Unknown	1	7	M	Greek	Artificial	Adequate	March
11	Deficient	Poor	13	8	M	Irish	Breast	Adequate	April
12	Unknown	Unknown	7	1	F	American	Artificial	Adequate	October
13	Deficient	Poor	5	4	M	Portuguese	Artificial	None	March
14	Unknown	Unknown	9	6	F	Italian	Breast	None	January

the others all had adequate artificial formulas with but three exceptions. Forty-three per cent of these babies received cod liver oil or a substitute in amounts ordinarily sufficient to prevent rickets. Infection was a prominent feature in the majority of cases but may have been the result rather than a predisposing cause of the development of rickets.

Accurate maternal history could be obtained in eleven of the fourteen cases. Fifty-five per cent, or six cases, had a history of five or more pregnancies in rapid succession. Data concerning the mother's health and dietary were ascertained in eight instances. Only one mother was definitely known to have had both an adequate diet and good health. In this case the infant was born prematurely and was a twin so that the florid rickets and multiple fractures seen in this baby are more readily understood. Four mothers had very poor health and diets that were definitely deficient, while in three others health was impaired but no details of the diets could be elicited. In two cases in which the maternal health and diet were exceptionally bad, the infants, in addition to multiple fractures, had thoracic and spinal deformities. These cases were somewhat similar to those reported by Park and Howland¹². Giant¹⁸ describes cases in young rats born of mothers with particularly defective diets, who developed extensive osteoporosis, multiple fractures, thoracic deformities, and kyphosis.

Calcium and phosphorus determinations in these cases with multiple fractures differed in no essentials from the figures obtained in usual cases of rickets. By roentgenogram all cases showed metaphyseal irregularity and cupping, but the outstanding feature in each case was a generalized osteoporosis of extreme degree. This characteristic is of interest in regard to an observation made by Toverud and Toverud¹¹. They had placed pregnant rats on a diet markedly deficient in calcium, but otherwise adequate, and found that the young of these mothers showed an extensive osteoporosis with multiple fractures but relatively little actual rachitic change in the metaphyses. One cannot postulate that the same mechanism prevailed in these infants with multiple fractures. However, there were antenatal factors present in a large number which were capable of exerting an influence on fetal metabolism. It would be most interesting if one could know the age at which rickets first developed in these babies who subsequently progressed to the stage of multiple fractures. It seems likely that a considerable portion would have shown rickets in the early months of life.

SUMMARY

A review of literature on early postnatal rickets and rickets with multiple fractures, together with a survey of 400 cases of active rickets and the determination of the incidence of early rickets and of rickets

with multiple fractures, permits an analysis of possible factors contributory to the development of these two forms of the disease

It is suggested that early postnatal rickets and florid rickets with multiple fractures may result from an insufficiency of stored skeletal calcium at the time of birth incident to nutritional and metabolic defects on the part of the maternal organism

A case of early infantile rickets with multiple fractures is reported

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2000 VAN NESS AVENUE

A RARE AND PECULIAR FORM OF ACUTE INTERSTITIAL PNEUMONIA

REPORT OF EIGHT CASES

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A RARE and peculiar form of acute interstitial pneumonia was discovered at autopsy in eight infants and children treated in the Jewish and Mount Sinai Hospitals during 1931 and 1932. Four of the cases were on the writer's service at the Jewish Hospital, two were on his service at the Mount Sinai Hospital, and two were on the service of Dr. Harry Lowenberg at the Mount Sinai Hospital.

CASE REPORTS

CASE 1—J. L., a five month old colored male infant, was admitted to the Jewish Hospital on Feb. 20, 1931, with dyspnea and grunting expiration which had developed the day previous, with a slight cough of several days' duration, and with fretfulness that had existed for a week.

The family history and the past medical history were negative.

The baby appeared very sick. The temperature was 103° F., the pulse was imperceptible, and the respirations were about 80 and very shallow. Some cyanosis and flaring of the alae nasi were present. There was no rachitic rigidity and no Kernig's sign. The lungs showed some impairment at the apices. The breath sounds were harsh and rough throughout, but there were no râles. The abdomen was slightly distended. A diagnosis of bilateral bronchopneumonia was made. A mustard plaster was applied over the whole chest. The child was given a colonic irrigation of a 5 per cent solution of sodium bicarbonate. Whisky, potassium citrate, and aromatic spirits of ammonia were administered by mouth. Two and three-quarters hours after admission the baby died.

The autopsy was performed by Dr. S. Levine, the surgical pathologist to the hospital, who made a diagnosis of bronchopneumonia, septicemia, and cloudy swelling of the liver and kidneys.

There was no effusion in either pleural cavity. The parietal pleura was studded with small pinpoint petechiae. The lungs presented numerous circumscribed areas of consolidation, sharply outlined and of increased consistency, sinking on being immersed in water. Very little pus could be expressed from the areas involved. The tracheobronchial glands were not enlarged.

The histologic examination was made by Dr. B. A. Gouley, the hospital pathologist. The lungs showed nonsuppurative pneumonitis. There was marked engorgement of the capillaries and infiltration of epithelioid cells throughout. The pleura was thickened by hemorrhage and edema. The alveoli contained fibrin and desquamated epithelium cells but no polymorphonuclear exudate. In many places they were empty. Associated with the interstitial thickening there was a certain

From the pediatric wards of the Jewish and Mount Sinai Hospitals, Philadelphia.
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degree of collapse, more marked in some fields than in others. The bronchi seen showed no definite pathology. This acute nonsuppurative interstitial pneumonitis was identical with that seen in rheumatic fever. Small foci of necrosis occupied the interstitial infiltration.

Culture of the heart & blood showed a short chain, gram positive diplococcus and gram negative diplococci (*B. coli*). It was impossible to isolate the organisms.

CASE 2.—E. J. a four month-old negro girl, was admitted to the Jewish Hospital on Apr. 8 1932. The baby had had a cold for a week with running nose and cough. On the day preceding admission the mother noticed the child was having difficulty in breathing and brought her to the accident ward where tentative diagnoses were made of (1) enlarged thymus, (2) laryngeal diphtheria, (3) foreign body in the air passages, or (4) edema of the larynx secondary to upper respiratory infection. After roentgen ray treatment over the thymus gland breathing became easier. X ray examination failed to reveal a foreign body but disclosed a small consolidation of the right lung. The trachea and larynx appeared clear and not displaced. Throat smear showed diphtheroids, and throat culture showed *Staphylococcus aureus*.

The child was sent home but did not improve and next day was admitted to the ward.

The child seemed very ill and had laryngeal stridor. The laryngologist and bronchoscopist at first regarded the case as one of laryngeal stridor but later decided against a definite laryngeal obstruction regarding the dyspnea as due to the pulmonary condition. The face and lips were extremely cyanotic and ashy in color. There was no nasal rigidity. The heart sounds were very rapid but of good quality. There was no murmur. The lungs showed evidence of slight consolidation posteriorly below the angle of the right scapula. The abdomen was moderately distended but not rigid. There was a slight umbilical hernia. No organs or masses were palpable. There was no eruption.

Throat smears on April 9 and 11 were negative for diphtheria bacilli. Throat culture on April 9 showed *Staphylococcus aureus*. Nasal culture on April 11 was negative for diphtheria bacilli and contained *Staphylococcus aureus* and *Bacillus proteus*.

The baby was placed in an oxygen tent with her head hyperextended in which position she breathed more easily. An intraperitoneal injection of 200 c.c. of Hartmann's solution, hypodermoclysis of 500 c.c. of normal saline solution with 50 c.c. of a 50 per cent solution of glucose and an asafetida enema were given. A rectal tube was inserted. The temperature, which was 101.8° F. on admission dropped to 101° and then rose steadily to 105.8°. Eight hours after admission cyanosis and laryngeal stridor were no longer present, and two and a half hours later the baby died.

The autopsy and histologic examination were made by Dr. B. A. Gouley who made a diagnosis of lobar interstitial and alveolar pneumonia. In the right upper lobe a firm greyish red pneumonic consolidation, the size of a 10-cent piece, was found occupying the lower half of the lobe. A similar but smaller lesion was found in the adjacent portion of the lower lobe and in the periphery of the left upper lobe.

Section of the lung showed the same type of very densely cellular lobar pneumonia that had been noted in other babies the preceding winter. The cellular infiltration was heavy, but in addition a much greater percentage of polymorphonuclear cells in the alveolar exudate than in the other cases was noted. Curiously most of the polymorphonuclear cells were broken up. A few alveoli contained

chiefly fibrin and red blood cells, and in some fields the interstitial involvement, and the variety of cells—endothelial, epithelioid, and polymorphonuclear—was striking

Postmortem smears of the lung showed many pneumococci, some pus cells, and no tubercle bacilli

CASE 3—M J, a negro girl, seven months old, was admitted to the Jewish Hospital on Apr 22, 1932

The family and past medical histories were negative

The child had had a cold for three weeks and had been grunting most of the time

The child appeared acutely ill and very toxic. She had a square head and a patent anterior fontanel, the sutures were not all closed. The respirations were very shallow and rapid, with grunting expiration. There was no movement of the alae nasi. Retraction of the interspaces and of the epigastrium was observed during inspiration. A rachitic rosary was present, and the wrists and ankles were enlarged. The heart was enlarged above and to the left. There was dullness on the right side anteriorly below the second rib, in the axilla below the third rib, and posteriorly above the third rib. On the left there was slight dullness over the whole chest anteriorly, marked dullness over the whole chest posteriorly, and slight dullness above the fifth rib in the axilla. Breath sounds were exaggerated on the right posteriorly, and there was slight bronchial breathing on the left posteriorly with crepitant râles at the base. The tonsils, pharynx, and both eardrums were slightly injected.

The hemoglobin was 40 per cent, and the red blood cell count was 3,150,000 with slight achromia, slight anisocytosis and occasional poikilocytosis. The leucocytes were 6,500 with 55 per cent neutrophils and 45 per cent lymphocytes. The temperature, which on admission was 103.6° F, dropped to 101.4° and then rose to 104.2°

The baby was given a course of calomel, followed by milk of magnesia, an asafetida enema, tincture of digitalis, whisky, and sodium citrate. Eight hours after admission 7½ grains of quinine and urea hydrochloride were injected intramuscularly. Fifteen minutes later the baby died.

The autopsy and histologic examination were performed by Dr B A Gouley, who made a diagnosis of interstitial lobar pneumonia.

The internal examination showed pneumonia of lobar dimensions, occupying the entire left lower lobe and the adjacent part of the right upper lobe. On section the consolidated tissue was greyish white, firm, and comparatively dry. There was no suppuration, and the bronchioles were moderately thickened. The tissue was tough as if a diffuse fibrosis or carnification was present. The lymph nodes were practically normal, and pleural reaction limited to small isolated patches of surface dulling. The right lung was congested.

Histologically there was a great karyorrhexis of polymorphonuclear and endothelial cells. Bronchioles were partially filled with an exudate containing broken down polymorphonuclear and endothelial cells. The alveolar cells were filled with red blood cells and fibrin, with a small number of these cells described. The pleural coat was not seen in the section examined. The liver showed a cloudy swelling and congestion. Another section of lung showed severe congestion and edema.

CASE 4—D A, a white boy, eight years old, was admitted to the Mount Sinai Hospital on Apr 19, 1932.

It was impossible to obtain the family history or the past medical history.

According to the patient's brother, the child had been fairly well until the day before admission, when he became sick and complained of a pain in his chest.

The child was semiconscious, restless and delirious, having had visual hallucinations. He was poorly nourished, with cyanotic lips and hands and cold and clammy skin and extremities. A rash was present over the chest and arms. The child was breathing very rapidly with apparent difficulty but there was no movement of the alae nasi and no retraction of the epigastrium or intercostal spaces. The neck was not rigid. The pupils were equal and reacted to light but the eyes were dull, and there was a scar over the right cornea. The pulse was barely perceptible. The cardiac boundaries were normal, and the heart sounds were weak. The whole right chest was dull on percussion, and the breath sounds suppressed, somewhat harsh and accompanied by some rales. The internæ had noted impairment at the left base with rather harsh breath sounds but no rales. The abdomen was distended and tympanitic. Kernig's sign was absent. Both legs, however, seemed to be rather spastic, and there was marked tenderness in the knee joints.

The child was placed in an oxygen tent and given 30 grains of quinine and urea hydrochloride intramuscularly 2 ampules of glucose intravenously 1 cc of pituitrin 1 dram of digalen and 1/30 grain of strychnine sulphate subcutaneously and milk of amfetida by rectum.

The child became very restless, yelling screaming and fighting the oxygen tent which in consequence was removed. Later the child became more quiet and tried to cough. The pulse became imperceptible the dyspnea and cyanosis increased and the boy died one hour after admission.

The autopsy and histologic examination were made by Dr David B. Meranze, who made a diagnosis of diffuse myocarditis, early interstitial pneumonia of both lungs, congestion of the thymus, cloudy swelling fatty degeneration and congestion of the liver congestion and edema of the pancreas, cloudy swelling and congestion of both kidneys and acute mesenteric lymphadenitis.

The left lung came away freely from the chest wall. The upper lobe was pinkish and on section showed a moderately congested, well aerated normal surface. The lower lobe was bulky and had a generally bluish cast. It contained less air than normally. On section it was purplish red in color markedly congested, had a suggestion of granularity and seemed somewhat more solid than normally. The bronchi of the lower lobe contained a small amount of a thin slightly purulent exudate. The lymph nodes about the hilum were deep purple in color and on section were markedly congested. The right lung showed the same involvement as that of the left lower lobe possibly to a less marked degree. The middle lobe alone seemed to have escaped the process described.

On microscope examination the lung was found intensely congested. The septums were greatly thickened by congestion and some degree of round cell infiltration. In some regions actual interstitial and even intraalveolar hemorrhage had occurred. Many alveoli were filled with edematous fluid, desquamated epithelium and some inflammatory cells. The pleura was thickened by edema.

CASE 5—C. O., a white infant girl, aged eight months, was admitted to the Mount Sinai Hospital on Dec 12, 1931.

The baby had been delivered at term with instruments and probably had been asphyxiated. She had been bottle fed from birth and was apparently gaining in weight. She had received three transfusions at another hospital for weakness and anemia but had otherwise been well never previously having turned blue or breathed rapidly.

One week before admission the baby suddenly developed a cough and high fever, which condition improved for a few days under treatment and then became worse. The spasm of coughing became so severe on the day preceding admission that the child turned blue. At times the cough produced vomiting.

The infant was markedly undernourished, looking like one three months old, rather than eight. She appeared acutely ill, with marked cyanosis, especially of the lips, some respiratory distress, and marked playing of the alae nasi. The temperature was 102° F, the pulse, 160, and the respiration, 72. The tonsils and pharynx were injected. There was no nuchal rigidity.

The cardiac boundaries were normal. The heart action was very rapid and irregular. The first sound was fair at the apex but poor at the base.

Examination of the lungs disclosed dullness bilaterally above the fourth rib, anteriorly, posteriorly and in both axillae, being more marked on the right posteriorly, also dullness on the right posteriorly below the sixth rib. Tactile fremitus was increased bilaterally over the upper lobes, to a less extent on the left. The breath sounds were somewhat harsh. Crepitant and subcrepitant râles were scattered throughout the chest. One examiner heard some fine crackles at the right base.

The abdomen was soft and not distended. The spleen was barely palpable. The liver was not enlarged. Kernig's and Brudzinski's signs were absent.

The hemoglobin was 65 per cent, the red blood cell count was 3,490,000, and the leucocytes, 29,400 with 60 per cent polymorphonuclears.

The child was placed in an oxygen tent and given liquids, glucose, sodium citrate, a mild mustard plaster around the chest, an emulsion of glycerin and asafetida, and drops in the nose of a 1:5,000 metaphen solution. Five grains of quinine and urea hydrochloride were injected intravenously. Four hours later the baby was given 2½ grains of quinine hydrobromide, 2 minims of digalen, 5 minims of brandy, and 5 grains of sodium citrate orally, but vomited them all. Five grains of quinine and urea hydrochloride were then injected intramuscularly. A Murphy drip of a 5 per cent glucose solution was started. Two hours later the temperature was 106.4° F, the pulse, 200, and the respirations, 80. The child looked very ill and toxic, was quite cyanotic, developed upward and lateral nystagmus, and vomited a prune juice material. An hour later the child went into convulsions and became exceedingly cyanotic, the heart sounds being very feeble, the respirations remaining 80. Two hours subsequently the temperature reached 107.8° F, the cyanosis became very marked, and râles were very evident throughout the chest. Death occurred two hours later.

The autopsy and microscopic examination were made by Dr. David R. Meranze, who made a diagnosis of cloudy swelling of the myocardium, fibrinous pleurisy, interstitial pneumonia of both lungs, diffuse hyperplasia and congestion of the spleen, congestion, cloudy swelling, and moderate fatty degeneration of the liver, congestion and cloudy swelling of both kidneys, and acute mesenteric lymphadenitis.

The left lung was free of adhesions and was about normal in size. The lateral aspect of both lobes, except for the upper half of the upper lobe, was externally reddish blue in color, non-air containing, and on section a mottled purplish color with a fleshy aspect and feel. There was a suggestion of degeneration in the exposed tissue. The remainder of the lung was pink and air containing. The bronchi were normal. The bronchial glands were also normal in appearance.

The lateral fringe of the lowermost portion of the upper lobe of the right lung and the lateral upper half of the lower lobe were also purplish areas, somewhat depressed and rather firmer than on the left lung. Small pinkish islands of tissue were scattered in these regions. On section the tissue was rather dry. Small, ochre-colored nodules were present, which seemed somewhat degenerated and separable from the remaining fleshy, purplish, involved tissue. The remainder of the lung, including the middle lobe, was practically normal. The hilar nodes were not involved.

On microscopic examination the pulmonary involvement was found to vary in kind and degree. In one area the process seemed of the lobar pneumonic type. In

other areas the process was most marked about the bronchi. In still others the alveolar septums were thickened by congestion and inflammatory reaction. The exudate was rich in polymorphonuclear cells but poor in fibrin. Intense congestion was everywhere a feature. Areas of collapse were present. The bronchi contained a purulent exudate. A fibrinous reaction was present in the pleura.

Bacteriology—Heart blood culture—*Staphylococcus albus*

CASE 6—J. M., a nine-month old white boy was admitted to the dermatologic service of the Jewish Hospital on Feb. 25, 1932 with eczema. His mother had had eczema in her infancy and the patient himself at the age of three years developed a very itchy exfoliative rash on the face, which had appeared and disappeared several times. Two months before admission the rash also appeared on the back and lower extremities, behaving like the face lesion. The baby had had many colds and for the three months preceding admission had had coryza and cough. The child suffered from frequency of urination, was irritable, slept all day and was awake all night.

Examination disclosed a rachitic baby with generalized papular eczema, producing excoriation of the glans penis, and with coryza and pharyngitis. Temperature pulse and respiration were increased. The heart and abdomen findings were negative. There was slight dullness over the right chest posteriorly, but there were no other abnormal chest signs. Dermatographia was present. The urino was normal. Skin protein tests proved negative. The hemoglobin was 71 per cent, the red blood cells, 4,500,000 and the leucocytes 6,500 with 42 per cent neutrophils, 55 per cent lymphocytes, 1 per cent transitionals, and 2 per cent eosinophils. The Wassermann test was negative. Blood calcium was 10 mg. X-ray examination showed both lung fields clear with no evidence of consolidation.

The eczema improved at first but later became pustular. Cervical adenitis and anemia developed. In addition to moderate dullness on the right posteriorly and in the axilla there developed a slight dullness on the left anteriorly and in the axilla. Eleven days after admission a right otitis media occurred and a month later double otitis media.

Five weeks after admission the child developed an acute upper respiratory infection with a fever of 104° F., increased pulse and respiratory rates, coryza, pharyngitis, and cough. Two days later he had a slight cough, grunting expiration and movement of the alae nasi. The heart was enlarged slightly to the left, and the heart sounds were fair. There was a diffuse red maculopapular eruption over the back and around the neck. Dullness was present over the whole right chest posteriorly and slight dullness in the right axilla with increased fremitus, but there were no other definitely abnormal chest signs. The hemoglobin content was 57 per cent, the red blood cell count was 3,500,000 with slight anisocytosis, slight achromia and occasional polkilocytosis, the leucocytes 22,100 with 67 per cent neutrophils, 32 per cent lymphocytes and 1 per cent large mononuclears.

Twenty-five grains of quinine dihydrobromide were given by mouth over a period of twenty-four hours, during which time the temperature dropped to 98.8° F. Twelve hours later the temperature rose to 103°, there was playing of the alae nasi and impairment was noted on the left chest posteriorly over the eighth or ninth rib. The right ear was found inflamed and a myringotomy was performed. An x-ray examination of the chest taken during the second temperature rise showed both lung fields absolutely clear throughout with no pulmonary pathology seen.

After three doses of 3½ grains each of quinine dihydrobromide, the temperature twelve hours later dropped to 99° F., where it remained for thirty-six hours, and then rose abruptly to 104°. The left eardrum found reddened and bulging was incised on the following day. A roentgenogram taken at this time showed consolidation in

the right upper lobe. Impairment was still present over the entire right lung, being more marked in the upper lobe. Dullness also was noted over the left lung, at first over the lower lobe, and on the following day over the upper lobe, associated with harsh breath sounds or tubular breathing and with crepitant râles. On the next day the child had a distressing cough, grunting expiration, marked movement of the alae nasi, and an inspiratory retraction below the costal margin. On the right chest there was dullness anteriorly above the second rib, in the axilla above the fourth rib and posteriorly above the fifth rib, all associated with increased fremitus and vocal resonance. There was dullness also on the left posteriorly above the fifth rib. The breath sounds could not be distinguished on account of the noise from the mouth and nose but on the following day they were noted as distant and tubular. No râles were heard.

Fourteen doses of 5 grains each and seven doses of $2\frac{1}{2}$ grains each of quinine dihydrobromide were given over a period of three and a half days, during which time the temperature first dropped to 101.4° F and thereafter fluctuated between 101.6° and 102.4° . The blood picture six hours after the last dose of quinine was the same as that taken previously, except that the neutrophils were 81 per cent, and the lymphocytes, 19 per cent. The temperature remained elevated for a day and a half longer until the patient died. During the last five days the pulse fluctuated between 140 and 172, and the respirations, between 30 and 60.

Blood culture showed pneumococcus Type IV.

In addition to $117\frac{1}{2}$ grains of quinine the baby received 2 minims of tincture of digitalis three times a day, nasal disinfection with a 1:5,000 solution of metaphen, inhalations of carbon dioxide and oxygen for ten minutes every two hours (the child later being placed in an oxygen tent), and, after the quinine was stopped, 5 minims of creosote carbonate every four hours.

The autopsy and histologic study were made by Dr B. A. Gouley, who made the diagnosis interstitial pneumonitis of the upper lobe of the right lung and cloudy swelling of the other organs.

The findings of chief interest were in the lungs. The right lung showed a complete consolidation of the upper and middle lobes. The remaining lower lobe, as well as the left lung, was practically normal. The consolidation was white or pinkish and yellowish white and unusually firm and dry. The cut surface was very smooth. In some areas the consolidation appeared to be the result of confluence of smaller lesions. No pus was noted, and the bronchial tree was moderately congested. The appearance of the pulmonary lesion was definitely unlike that of the ordinary pneumonias. The mediastinal lymph nodes were of normal appearance.

On histologic examination numerous lung sections showed complete consolidation although the density of cellular infiltration varied in different fields. There was an irregular interstitial infiltration, very marked in some fields and minimal in others. It consisted of rather large round cells and also irregular epithelioid cells, these two types were usually associated with each other, sometimes forming large isolated nodules, usually perivascular, that tapered out interstitially or else broke into the alveolar spaces, filling and obliterating them. Occasionally multinucleated cells were seen in these nodules. Small groups of very irregular epithelioid cells were often clustered around small foci of fibrinous (fibrinoid) necrosis.

The alveoli were filled with fibrin, some contained no cells or very few, but in other fields there was a heavy alveolar infiltration. This alveolar exudate contained only a small percentage of polymorphonuclear cells, and in many alveoli apparently none were present. The cells were often very small or fragmented and of irregular shapes, suggesting a strong similarity to the interstitial infiltration. In some large areas this cellular invasion was so dense that the entire lung structure was ob-

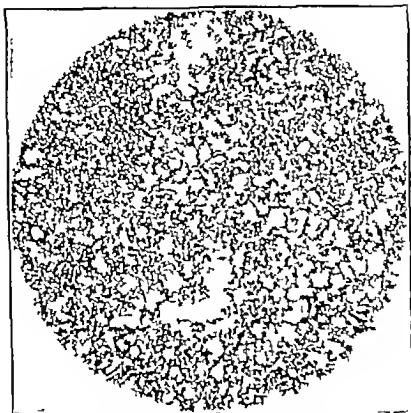


Fig. 1.—Acute interstitial pneumonia ($\times 61$) Case 6. Note the thickened alveolar walls and the "pouring over" of the exudate into the alveoli. In the upper left quadrant the infiltration is heavy. In other places the alveoli are filled with fibrin or serum.

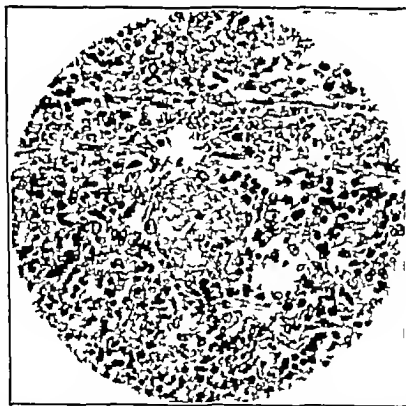


Fig. 2.—Acute interstitial pneumonia ($\times 490$) Case 6. Note interstitial (interalveolar) infiltration of round cells and "epithelioid" cells and the invasion of the alveolus (lower left) by the same type of cells.

secured. The fibrin here had a granular stippled appearance. In many fields, but especially in these densely cellular areas, the alveolar walls had been converted into strips of fibrin ("fibrinoid" degeneration).

This very cellular infiltration with its fibrinous degeneration of the alveolar walls was not an abscess formation, not only was this conclusion drawn from knowledge of the gross appearance, but from the absence or near absence of polymorphonuclear cells.

In a few fields there were noted small isolated groups of alveoli where the exudate consisted of fibrin, desquamated alveolar cells, and a small to moderate number of polymorphonuclears. The alveolar walls here were not infiltrated, and in these small areas the pathology was apparently entirely different from that noted above and was of the type normally associated with pneumococcus infection. The small bronchioles were filled with a very cellular exudate, identical with that seen in the largest portion of the section. The bronchiolar mucosa and wall were intact throughout and the exudate in the lumen was very likely an aspiration from the alveoli rather than a true bronchiolitis.

The larger blood vessels, particularly branches of the pulmonary artery, often showed small necrotic foci of epithelioid cells in the adventitia and media. One large vessel was recently thrombosed.

The interalveolar capillaries were markedly congested but where the fibrinous degeneration of the alveolar wall was more or less complete, they had disappeared.

The following two cases occurred on the service of Dr. Harry Lowenberg at the Mount Sinai Hospital and are reported with his permission.

CASE 7—E. S., a six month old white girl, was admitted Dec. 7, 1931. The baby, born two weeks prematurely, probably had been asphyxiated and had had a collapsed lung. During the three days preceding admission the child had vomited, had high fever, had a slight cold and cough, and had suffered some loss of weight.

On admission the temperature was 104° F., the pulse, 160, and the respiration rate, 48. The child looked acutely ill and was very flabby and below the normal weight. The respirations were not labored, nor was there playing of the alae nasi or cyanosis or cough. The nose, ears, and throat were practically negative. The heart was negative. The lungs exhibited no definite abnormal signs. The abdomen was practically normal.

X-ray examination on the day of admission showed an irregular consolidation of the lower portion of the right upper lobe, which on the following day showed some extension. Three days later x-ray plates disclosed in addition an incomplete consolidation of the left upper lobe.

The hemoglobin was 70 per cent, the red blood cells, 3,900,000, and the leucocytes, 20,400, with 65 per cent polymorphonuclears, 34 per cent small lymphocytes, and 1 per cent large lymphocytes.

On the day following admission the temperature dropped to normal, the condition seemed better, and the physical signs were all indefinite as to clinical pneumonia. Two days later the temperature went to 106.6° F., the pulse, to 200, and the respiration rate, to 80, but the chest was still negative, according to physical signs, and the ears, nose and throat were negative. The following day the child looked very much worse, and pathology could be demonstrated in both lungs, mostly in the right. The baby grew progressively worse, the temperature rose to 108° F. and the respiration rate to about 90, the pulse being too rapid to count. The baby became very cyanotic, but the heart sounds remained of fairly good quality, al-

though the first and second were alike. Râles were heard on both sides anteriorly and posteriorly. Pulmonary edema set in, cyanosis became more marked, the heart sounds became poor, there developed marked respiratory embarrassment and death ensued.

Treatment consisted of the use of an oxygen tent, cooling bath, sodium citrate, glycerin asafetida enemata, normal saline by hypodermoclysis, atropin, pituitrin, and the insertion of a rectal tube.

The autopsy and the microscopic examination were made by Dr. Meranze, who made the diagnosis of interstitial pneumonia of both lungs, congestion, cloudy swelling and some fatty degeneration of the liver, congestion of the spleen, and marked congestion and moderate cloudy swelling of the kidneys.

The left lung was of normal size, with no adhesions. No pleurisy was present. The outer half of the upper and lower lobes, a somewhat pyramid shaped area, the apex of which was the hilus, was semisolid and purplish in color. The overlying pleura was injected and irregularly blotched with minute ecchymoses. This region on section had a reddish purple aspect and was fleshy. Medial to it was a narrow fringe of depressed bluish tissue. The remainder of the lung was normal. The bronchi and hilum nodes were normal.

The entire lower lobe and the outer half of the middle lobe of the right lung were similarly involved in a fleshy non air-containing, reddish purple process over which the pleura was injected. Here and there on section in the involved area was seen a small intensely reddish purple area, almost nodular in outline.

On microscopic examination the pleura was uninvolved. Very little of the lung studied was normal. Congestion was marked throughout. Large areas were involved in an inflammatory process which was predominantly interstitial and in which round cells and plasma cells were predominant. In some regions exudate into the alveoli was present, and there the exudate was often scanty in cells, containing some polymorphonuclears and relatively dense in fibrin. In other areas the alveolar exudate was dense. Hemorrhage was a striking feature and was present interstitially and within many alveoli. Some of the smaller bronchi contained cellular exudate, the larger branches were clear. Many sections of lung showed collapse and compensatory emphysema.

CASE 8—A. V., a white male baby thirty three months old, was admitted Dec. 9, 1931.

The birth was normal, but the delivery was instrumental, the labor being dry. The baby was breast fed for nine months and had had no feeding difficulties. He had had measles, an abscess under the chin and frequent colds, but no sore throat.

He was well until the day before admission, when with no apparent cause he started to vomit—at first mucus, later greenish water. He was very feverish. At 1 A.M. on the day of admission he had a convulsion accompanied by loud screaming lasting about five minutes. The temperature was high, and he was delirious all night, dozing for short periods and drinking fluids copiously. He had another convulsion at 4:30 P.M. after which he was admitted to the hospital.

On admission the temperature was 107° F., pulse 200 and respirations, 38. He was acutely ill, semicomatose, breathing rapidly and showing an expiratory grunt. The head and ears were negative. The eyes were staring, the pupils were equal and reacted to light and accommodation. There was some left lateral nystagmus. The nose was normal, the pharynx, injected and the tonsils, enlarged. There was no adenopathy or rigidity of the neck. The heart showed accentuation of the pulmonary second sound but no murmurs.

Over the right chest percussion was impaired, and there were some small rather indefinite râles

The abdomen showed some distention, but no tenderness or rigidity

The liver and spleen were not palpable The knee jerks were exaggerated, especially on the right There was a suggestion of Kernig's sign on the right

Some three hours later, although the child was critically ill, semiconscious, stuporous and feverish, the respirations were not labored, and there was no playing of the alae nasi and no grunting Heart and lungs were found negative There was no nuchal rigidity, Babinski's sign, or ankle clonus Brudzinski's contralateral sign was present, and at times Kernig's sign was positive Later there was general trembling of the body when the child moved or turned, and the lower extremities in general were spastic Spinal puncture revealed a clear fluid under moderately increased pressure The leucocytes numbered 29,300, with 94 per cent polymorphonuclears, 4 per cent small mononuclears, and 2 per cent large mononuclears The spinal fluid was negative The blood sugar was 130 There was no growth on blood culture The blood calcium was 10.2 mg X-ray examination showed no evidences of pulmonary consolidation or pleural effusion

The following day a few sticky râles were heard at the end of inspiration over the left lower base posteriorly There was also some evidence of tetanic spasms Later in the day impaired resonance was noted just above the left base posteriorly, with harsh breath sounds and occasional râles on inspiration.

X-ray pictures showed a suggestion of an early pneumonia in the left base behind the heart, which evidence was too incomplete for definite diagnosis

During the night the child had a convulsion On the next day the physical signs of consolidation of the left lower lobe were much more distinct

Twelve hours later the patient was very ill, with temperature over 108° F, and was very cyanotic He became rigid at times and at times assumed opisthotonos The eyes were glazed and half closed The chest was full of large gurgling râles The heart sounds were of poor quality and embryocardiac and became weaker, though there was no pulmonary edema, the baby died Spinal puncture was made an hour before death and 12 cc of clear fluid were obtained under slightly increased pressure

The autopsy and microscopic studies were made by Dr David R Meranze, who made a diagnosis of congestion of the right lung, interstitial pneumonia of the right lung, congestion of the spleen, cloudy swelling of the liver with congestion and edema, and congestion and cloudy swelling of the kidneys

The upper lobe of the left lung was normal The pleura of the outer two thirds of the lower lobe was dulled and thinly covered by a readily removable greenish layer of fibrinous exudate The underlying lung tissue was firm and non-air containing The extreme lowest fringe was especially firm The involved lung area on section had a swollen purple fleshy aspect and in which area there was much blood. The harder lowest fringe just mentioned was pinkish and entirely dry and rubbery in consistency The bronchi and hilum nodes were normal

The right lung weighed 180 gm It was large, pink and air-containing Its bronchi and glands were normal

On microscopic examination the tissue of the right lung was merely congested as was also some of the uninvolved portions of the left The involved portions showed predominantly a hemorrhagic type of interstitial pneumonia in which the cellular exudate contained few polymorphonuclears In some regions the exudate was alveolar, but here, too, the interstitial tissue was involved Marked congestion and areas of collapse were present Some of the veins contained purulent material The pleura was the seat of an acute fibrinous pleuritis.

Two cases of pneumonia that I treated at the Mount Sinai Hospital, in which recovery took place, I believe to be instances of acute interstitial pneumonia, but as this is impossible to prove, they have been omitted. One was in a fourteen month-old girl, who was given a total of 70 grains of quinine, and the other, in a boy, one year old, who received in all 57½ grains of the drug.

ANALYSIS OF THE CASES REPORTED

The most characteristic common feature in the eight cases reported is the histologic appearance of the areas of interstitial pneumonia. Most of the cases showed a capillary engorgement and an infiltration of round cells and epithelioid or plasma or endothelial cells and in some instances polymorphonuclear cells which was not abscess formation (Figs. 1 and 2).

The feel of the affected portion of the lung is also characteristic, being more like that of muscle than lung tissue. This does not always appear from the descriptions, which employ the terms 'firm', 'fleshy', 'rubbery', 'bulky', 'of increased consistency', 'semisolid', 'more solid than normal', and 'tough, like a diffuse fibrosis or carnification'.

The color of the affected portion of the lung was peculiar, being variously described as blue purple pinkish greyish red ochre greyish yellow, greyish white, and white.

A noteworthy circumstance was absence of suppuration.

There was nothing characteristic about the location of the lesions which was given in seven of the cases. The right upper lobe was involved in five cases, the right middle lobe in two, the right lower lobe, in four, the left upper lobe in three, and the left lower lobe in five.

Pleural involvement was rare, absence of excess fluid in the pleural cavity being marked in five cases. Fibrinous exudate was observed in only one case although there was dulling in another case and studding with minute ecchymoses in two cases.

Culture of the heart blood was made at autopsy in one case with growth of *Staphylococcus albus*.

The clinical course of the disease, the symptomatology, the physical findings, the roentgenologic examination, and the laboratory tests as observed in the cases reported, present nothing that can be regarded as characteristic of this peculiar form of acute interstitial pneumonia or as distinguishing it from other forms of pneumonia. This may be due in part to the paucity of cases and to the brief stay in the hospital of most of the patients, half of whom died within twelve hours after admission.

The most prominent clinical features are the short duration of the disease in most of the cases, the virulence of the infection, its fatality and its failure to respond to treatment. The ages of six of the patients

were between four and nine months. One child was thirty-three months old, and one was eight years old.

The duration of the disease in the eight cases was two, four, seven, eight, eight, nine, ten, and eleven days, respectively. The onset was sudden in five of the cases. The acute interstitial pneumonia was preceded by an attack of coryza in two cases.

The initial symptoms were cough in five cases, coryza in four, fever in four, grunting respiration in two, vomiting in two, and pain in the chest, fretfulness, delirium, laryngeal stridor, convulsions, and movement of the alae nasi in one case each.

Symptoms exhibited after admission to the hospital were cyanosis in six cases, cough in five, dyspnea in five, a grunting respiration in four, coryza in four, movement of the alae nasi in three, semiconsciousness, inspiratory retraction of the chest, convulsions, skin eruption, and nystagmus in two each, and pain in the chest, delirium, vomiting, and laryngeal stridor in one case each.

The highest temperature in each case was 108°, 107°, 106.8°, 105.8°, 104.6°, 104.2°, 104°, and 103° F, respectively.

The highest pulse rate in each case was 200, 200, 200, 172, 148, and 124, respectively, while in two cases the pulse was imperceptible.

The highest respiratory rate in each case was 88, 86, 82, 80, 60, 60, 54 and 48, respectively.

Dullness on percussion was noted in every case, increased fremitus in two cases, increased vocal resonance in one case, suppressed breath sounds in one case, harsh or rough breath sounds in six cases, and râles in six cases.

Distention of the abdomen occurred in four cases.

The hemoglobin varied from 40 per cent to 70 per cent, the red blood cells, from 3,150,000 to 3,900,000, the leucocytes, from 6,500 to 29,400, and the polymorphonucleus from 55 per cent to 94 per cent. Blood cultures during life are recorded in only two cases—*Pneumococcus* Type IV growing up in one, while the other showed no growth.

Resistance to treatment was characteristic of these eight fatal cases. Of special significance to me was the resistance to quinine therapy, which is in marked contrast to my experience with the use of quinine in cases of ordinary lobar and bronchopneumonia in both children and adults¹ in whom quinine has seemed to have a decided effect in combating the toxemia, favorably affecting the general symptoms, and shortening the course of the disease.

CRITICAL REVIEW OF THE LITERATURE ON INTERSTITIAL PNEUMONIA

Considerable confusion exists in medical literature on the subject of interstitial pneumonia. This term has been applied to a number of different conditions which have not always been clearly differentiated.

Some authors, while discussing one type, quote cases reported by a writer who is describing a different type, apparently without recognizing this fact. Moreover many different names have been employed to indicate the same process and the same designation has been used for different processes. In searching for references to the peculiar form of acute interstitial pneumonia here reported it therefore became necessary to study carefully in the published articles the macroscopic and histologic descriptions of the lungs regarded as being affected with interstitial pneumonia.

Chronic interstitial pneumonia is the form most frequently mentioned in the textbooks. It was described first by Corrigan, who called it *cirrhosis of the lung*.² It since has accumulated a variety of characterizations: interstitial pneumonia, chronic interstitial pneumonia, interstitial chronic lung inflammation, productive interstitial lung inflammation, pleurogenic interstitial pneumonia, productive fibrous pneumonia, chronic fibrous pneumonia, fibroplastic pneumonia, productive fibroplastic pneumonia, productive pneumonia, chronic pneumonia, indurative pneumonia, chronic indurative pneumonia, infiltration of the lung with induration matter, collapse induration, pneumonoconiosis, pulmonary sclerosis, pneumonia fibrosa chronica, carnification, inflammatory carnification, contracted lung, fibroid phthisis pneumonia with organization of the exudate, ulcerative pneumonia, parenchymatous pneumonia, lymphangitis reticularis, lymphangitis trabecularis, lymphangitis nodosa, and fibrous perivascularitis. This includes the types described by Walshe,³ Delafield,⁴ Heitler,⁵ Jacobi,^{6, 7} Feer,⁸ von Jürgensen,⁹ and von Hönsemann.¹⁰ In 1884 Heitler made the statement that all German authors previously had regarded interstitial pneumonia as chronic.

A subacute interstitial pneumonia also has been noted by Heitler,⁵ Jacobi,⁷ and others, the first including it under his primary parenchymatous pneumonia. Finkler¹¹ quotes Hanan as calling it progressive, intraalveolar indurated pneumonia and Orth as naming it pneumonia with organization of the exudate. Jacobi⁷ prefers the term 'pulmonary hyperplasia with secondary cirrhosis'. This form is regarded by Wagner,¹² Eppinger (quoted by Heitler⁵), and Hanan (quoted by Finkler¹¹) as a primary independent disease of the lung parenchyma which develops independent of other affections of the lungs and independent of any affection in the organism whatsoever. On the other hand Marfan,¹³ Finkler,¹¹ Eichhorst,^{14, 15} Gluzinski (quoted by Finkler), Hershe and Woronichin (quoted by Heitler), and Marchand (quoted by both Heitler and Finkler) believe it is an outcome of a croupous pneumonia, a view which Henoch¹⁶ questions.

Acute interstitial pneumonia is rarely referred to in textbooks on pathology, pediatrics, and medicine but is discussed more frequently in monographs and medical journals. Several distinct forms have been

described although the same distinctions are not recognized by all the different observers

Acute interstitial bronchopneumonia following measles, pertussis, diphtheria, and other infectious diseases with respiratory involvement has been noted by Bartels¹⁷ Kiomayer,¹⁸ Marfan,¹³ Honl,¹⁹ Koester,²⁰ Steinhaus,²¹ Hart,²² Jochman and Maltiecht,²³ Feer,⁶ MacCallum,²⁴ Opie, Blake, Small and Rivers,²⁵ Holt and McIntosh²⁶ and Hecht,²⁷ the last-named calling it giant-cell pneumonia, a classification regarded by Karsner and Mejeis²⁸ and Moore and Gross²⁹ as not justified. Preferable designations are the terms "focal pneumonia with peribronchial extension," according to Lauche³⁰ and "bronchogenous focal pneumonia," and "bronchopneumonia with peribronchial extension," according to Kaufmann^{31 32}

An acute interstitial pneumonia following, or occurring in, influenza, especially during severe epidemics, is looked upon by some writers as identical with the type just mentioned and by others as a different form. Hosack,³³ Hudson,³⁴ M'Reynolds,³⁵ Stearns,³⁶ and Mann³⁷ described cases they observed among soldiers and civilians during the War of 1812 and MacCallum,²⁴ Wolbach,³⁸ and Opie, Blake, Small, and Rivers²⁵ studied cases occurring in the army camps during the World War. This form of pneumonia has been variously termed pneumonia notha, peripneumonia notha, pneumonia typhoides, peripneumonia typhoides, typhoid pneumonia, primary streptococcus pneumonia, erysipelatous pneumonia, erysipelas of the lung, bilious pneumonia, putrid pneumonia, and malignant pleurisy. Kuczynski and Wolff³⁹ include lymphangitic or interstitial pneumonia among the grippal forms of pneumonia, while the term "focal pneumonia with peribronchial extension" is applied by Lauche³⁰ to this form as well as to the one previously discussed.

Lymphangitic pneumonia is the only true form of interstitial pneumonia, according to von Hönseman,¹⁰ Lauche,³⁰ and Kaufmann^{31, 32}. Several types of this form were tabulated under "chronic interstitial pneumonia." A number of different designations occur also in the acute types, including interstitial lymphangitic pneumonia, pleurogenous pneumonia, lymphangitis exudativa, lymphangitis proliferans, acute lymphangitis, peribronchial lymphangitis, peripneumonia, suppurative pneumonia, suppurative peripneumonia, perilymphangitis, perivascularitis, suppurative interstitial lung-inflammation, suppurative fibrinous pneumonia, suppurative peribronchial lymphangitis, pleurogenous interstitial pneumonia, peribronchial pneumonia, serofibrinous interstitial lung inflammation, and pneumonia desiccans. This is the form of interstitial pneumonia in the cases described by Smith and Langmann.^{51 52}

None of the descriptions of the various forms of interstitial pneumonia enumerated above fits the cases here reported, although in one of two types of influenzal pneumonia observed by Wolbach³⁸ at Camp

Devens, Mass., the lung tissue in patients dying within a few days after the onset of pulmonary signs was dark red and meaty in consistency."

The peculiar form of acute interstitial pneumonia exhibited by the cases here reported therefore, would seem to be extremely rare. The only references to conditions closely resembling it that I have been able to find are in articles by Corrigan⁴⁰⁻⁴⁴ Stokes⁴⁵ Gordon⁴⁶ Leichtenstern,⁴⁷ 48 and Buhl (quoted by Leichtenstern⁴⁷ 48), in the fifth and subsequent editions of George B. Wood's *Practice of Medicine*,⁴⁹ in which Gordon is quoted and in a recent report on rheumatic pneumonia by Gouley and Liman.⁵⁰ These conditions have been termed blue pneumonia, acute induration of the lung, asthenic pneumonia, acute lobular cellular pneumonia, acute lobar desquamative pneumonia, inflammatory carnification and rheumatic pneumonia.

Leichtenstern⁴⁷ 48 describes a rare but important clinical form of cellular pneumonia occurring in influenza and other infectious diseases such as scarlet fever, whooping cough and measles which he calls acute lobular cellular pneumonia and which he states has absolutely nothing to do with the so-called primary streptococcus pneumonia. "It often arises acutely," he says, "like a croupous pneumonia and attacks immediately a whole lobe, generally the upper lobe. Clinically it gives the impression of a croupous lobar pneumonia until postmortem examination discloses its true character. The cut surfaces of the lung are entirely smooth, homogeneous of a fleshy red to a bluish red color, of a fleshy, elastic consistence and totally devoid of air. Neither fluid nor air can be expressed nor do drops of pus flow from the severed bronchi. It is a great error to assume that these acutely arising lobar infections are formed by the confluence of lobular areas or result from an ordinary bronchopneumonia. They belong neither clinically nor pathologically to the latter. Histologically the pneumonia is characterized by extreme vascularity. The alveolar septums are broad and the seat of round cell infiltration; the lumina of the alveoli are filled with cells, but only traces of fibrin can be detected. The cells consist of a small number of red blood cells, the larger number of leucocytes but notably large epithelioid cells, which we believe to represent desquamated alveolar epithelium. This peculiarity differentiates it from a purely histologic point of view from the usual catarrhal pneumonia which on account of the large number of leucocytes, represents pus formation in 'optima forma' as Pfeiffer terms it. The acute lobar desquamative pneumonia described by Buhl which has unjustly been forgotten is clinically and pathologically almost identical with the form which we are now considering, namely the acute lobular cellular pneumonia. On account of the fleshlike consistence of the infiltrated lobe we have in the past used the expression 'inflammatory carnification.' We must, however, now withdraw this name as Weichselbaum and Knndrat have lately used it

to designate something quite different, namely, chronic indurative process Rusty sputum is never seen. The appearance of this sputum alone makes the differential diagnosis from croupous pneumonia possible, no other sign is absolutely pathognomonic "

In 1841 both Corrigan^{40 41} and Stokes⁴⁵ exhibited before the Pathological Society of Dublin specimens of a rare form of pneumonia then prevalent, presenting a number of remarkable characteristics Other cases were reported by Corrigan^{42, 43 44} and by Gordon⁴⁶ during a similar epidemic some years later Stokes regarded the disease as an acute induration of the lung differing from ordinary pneumonia Corrigan called it blue pneumonia at first and later asthenic pneumonia

The following is the description of these observers

The color of the lung when first seen after opening the thorax was a deep blue, bordering on purple, like a dark blue plum This appearance, however, was very evanescent, fading away rapidly and being almost completely lost in the course of three or four hours, the lung then becoming grey or iron grey in color

The lung was firm and solid, and exceedingly heavy and tough, but had none of the characteristics of acute hepatization from pneumonia and did not pass into the state of red or grey hepatization, the disease having no tendency to terminate in hepatization or suppuration At times the lung was friable or brittle, at other times requiring the greatest force to break it down The lung did not crepitate under the finger, thus differing from the first stage of ordinary pneumonia. When grasped in the hand, the lung felt like muscle, resembling carnified lung, but differing from it in retaining its original bulk It sank in water It did not pit on pressure, nor did it appear as much swelled as is usual in ordinary cases of pneumonia.

When cut, the lung did not exude any quantity of blood The cut surface did not exhibit the granular surface of ordinary pneumonia Where a section of the lung was made the color was iron grey, somewhat like that of the lung in the vicinity of gangrenous spots

In this early stage the disease seemed to be a simple congestion of the capillary vessels. There was no effusion of lymph, no tendency to pass into the second stage, no trace of purulent matter anywhere The congestion was of a peculiar kind, there was no exudate of serous or bloody fluid It was accompanied with that state of vessels characterized as the state of passive congestion Corrigan believed it to be a state of the lung in which the vessels are too weak and too much distended to be capable of contracting and regarded this atonic state of the vessels as one of the characteristics of the disease.

The disease proved fatal either directly in the first stage of congestion—in which it was, indeed, a very fatal disease, the patient dying when the lung was gorged and dark—or it passed from the first into the third stage, scarcely showing at all the second or hepatized stage According to Gordon, the lung seemed readily to pass into a condition somewhat allied to gangrenous degeneration with effusion into the bronchial tubes, the patient dying of asphyxia. The lung then was of a dirty grey color, there was no well marked suppuration, but a species of general softening, and commencing decomposition.

The clinical descriptions by Corrigan and Gordon cannot be said to give a characteristic picture of the disease, enabling one to distinguish

it from other forms of pneumonia. In several aspects, however, they bear some resemblance to the cases reported here.

According to these descriptions, the peculiar features of the disease were its assuming a bad and intractable character, its resistance to treatment, and its very rapid progress (some patients dying within a few hours from the onset of the attack), and the fact that the disease seldom extended over a period of weeks. Another feature, according to Corrigan, was shortness of breath, which is described by the patient as his most prominent symptom. The respiration may remain at 60, and some times is chiefly abdominal. The most remarkable feature in some of the cases was the great depression of strength, in no disease, Corrigan said, could the asthenic character be better marked. Indeed asthenic pneumonia was the name this author³ gave to this type, and George B. Wood⁴ placed under asthenic or typhoid pneumonia the reference to Gordon's article which he inserted in the fifth edition of his *Practice of Medicine*. A child under Stokes's care died of exhaustion. Among the symptoms of those dying in the early stage Gordon lists excessive weakness, great depression of strength, great and sudden collapse, sudden lividity, and coldness of the skin, the face becoming purple and a dark flush arising on the face.

Some of the characteristic findings in the Dublin cases were not observed in the cases here reported. In the former the disease occurred at all ages and was found most frequently in the upper lobes.

A distinguishing symptom, according to Gordon, was the cough, which was altogether different in character from that of ordinary pneumonia, being very short, frequent, and performed without any apparent muscular effort whatsoever—very unlike the painful and distressing cough so often witnessed in vesicular pneumonia. However, a boy under Corrigan's care who had a cough said he was afraid to cough owing to the pain it caused in his side.

Another distinguishing feature, according to Gordon, was that seldom was there much pain in the side, never the acute stabbing pain from the implicated pleura experienced in vesicular pneumonia, because pleurisy was rare.

In 1841 Stokes and Corrigan both stated that there were no symptoms of pleuritis, but in 1857 the latter said, 'Pain is variable and appears to depend altogether on the degree of inflammation of the pleura, most generally, however, it is not much complained of.'

High fever, which attends vesicular pneumonia, was absent, according to Gordon. Corrigan says that the patient in this treacherous disease often does not seek admission into a hospital nor advice in private practice until too late, being deceived by the absence of pain, fever, and expectoration and feeling merely debility and shortness of breathing.

The pulse seldom was remarkably frequent, according to Gordon. It was always feeble and soon acquired a peculiar jerking feel. Yet in

those who died in the early stage, he described the pulse as small, feeble, and very rapid. The skin was of its natural temperature, or cooler than natural, and the face was rather sallow or yellow.

Both Corrigan and Stokes in 1841 noted as a peculiar and marked feature of the disease that it was not amenable to any of the usual modes of treatment. Since 1856, however, Corrigan and Gordon treated it with quinine in large doses with satisfactory results, the former recommending strongly its main treatment by quinine. Gordon believed that quinine evidently exercised a specific power over the disease. After thus treating for eight months all the cases of this form of pneumonia which he had witnessed, and having had the opportunity also of observing several cases similarly treated by Corrigan, he stated that the result of this treatment has been that, of the cases which came under observation before effusion had taken place into the bronchial tubes, none proved fatal, while some few recovered, even after the lips had become blue, the face congested, and mucous râles were audible in the bronchial tubes. This experience is quite at variance with mine, although I gave much larger doses of quinine than did Corrigan and Gordon.

In the cases of rheumatic pneumonia examined by Gouley and Eiman,⁵⁰ the gross and histologic pathology revealed pulmonary changes which apparently had not been previously described but which in certain particulars bear some resemblance to those seen in the cases here reported. The lesion is described as an acute interstitial inflammation, with no considerable exudate of polymorphonuclear cells. The color of the affected portion of the lung in six of the nine cases studied was deep blue, dark blue, slate blue bluish, and dark red blue, respectively. The majority of the specimens showed but few lesions of their pleural surfaces.

SUMMARY

A rare and peculiar form of acute interstitial pneumonia was discovered at autopsy in six infants and two children. The most characteristic feature is the histologic appearance of the affected portions of the lung which present capillary engorgement and infiltration of round cells, epithelioid or plasma or endothelial cells, and in some cases polymorphonuclear cells, which is not abscess formation. Other characteristic features are the musclelike feel of the affected portion of the lung and its peculiar color. The cases studied presented no characteristic clinical, roentgenologic, or laboratory findings by which they could be recognized during life. The most prominent clinical features are the commonly short duration of the disease, the virulence of the infection, its fatality, and its failure to respond to treatment.

Of all the writers on interstitial pneumonia Leichtenstern, Buhl, Stokes, Corrigan, Gordon, and Gouley and Eiman are the only ones found by the author to describe conditions closely resembling this peculiar form of acute interstitial pneumonia.

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2110 SPRUCE STREET

TRACHEOBRONCHIAL OBSTRUCTION PRODUCED BY TUBERCULOUS LYMPHADENITIS

REPORT OF A CASE IN A TWO MONTH OLD INFANT

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ALTHOUGH miliary tuberculosis is not uncommon in infants the type of pathology observed in the following case together with the unusual clinical symptoms encountered present a picture deemed worthy of report

CASE REPORT

F H., white male, aged two months was born in Multnomah County Hospital, March 11 1934 The father and mother were in good health. There were four other children, aged seven, six two and one years. These were all well. There was no history of tuberculosis in the family and no known tuberculous contact The mother a Wassermann test was negative. Labor and delivery were perfectly normal. Birth weight was 3,100 gm. Subsequent examinations and course in the nursery were normal. The baby was brought in to the out patient clinic for regular monthly examination on April 12 He was nursing well and weighed 4420 gm. Physical examination was entirely negative at this time He was started on orange juice and cod liver oil.

On May 13, 1934, the baby was admitted to Doernbecher Memorial Hospital for Children with the history of having had a cold for about a week. He coughed considerably and was given nose drops. The previous day he began to have labored respirations. The baby was unable to nurse the following morning and consequently was brought to the hospital.

Examination.—The baby was well developed and nonnursed. He was having rapid, noisy respirations with an expiratory grunt. The color was good he was alert and did not appear critically ill. Rectal temperature was 98.6 F. There was no evidence of inflammation or foreign body about the upper respiratory passages. There was marked sternal retraction with each respiration. Chest percussion revealed slight impairment over both apices. Breath sounds were roughened with an expiratory wheeze over the left chest and diffuse rales throughout both sides of the chest. The abdomen was not distended, and there were no masses palpable. The spleen was not palpable below the costal margin. Extremities were normal reflexes active.

Urinalysis was negative. Blood examination revealed hemoglobin 53 per cent (7.6 gm.) erythrocytes, 2,300,000 per c.mm. leucocytes 11,500 per c.mm. with the following differential count polymorphonuclear leucocytes, 49 per cent, eosinophiles, 1 per cent small lymphocytes 24 per cent; monocytes, 11 per cent, staff cells 15 per cent. Mantoux test (0.1 mg) was negative.

Radiographs of the chest on May 15 and May 20 failed to reveal any evidence of opaque foreign body. There was a widening of the mediastinal shadow suggesting enlargement of the thymus gland. The left diaphragm was markedly elevated.

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heart, pulled well over to the left side, right hilum, congested, there was some infiltration in the right upper lobe (these findings were reported as strongly suggesting a pneumonia in the right upper lobe area)

Course—Shortly after admission the respirations became much more labored and the baby became quite cyanotic. He was placed in an oxygen tent and given subcutaneous fluids because gavage attempts seemed to increase the cyanosis. Temperature ranged from 98.2° to 101.2° F, staying fairly close to normal most of the time. Lung findings remained about the same, with bronchial breath sounds heard over the right apex and marked impairment to breath sounds over the left apex. Râles persisted throughout. The color improved somewhat while he was in the oxygen tent. But since the baby became quite restless and seemed to do as well out of the tent, the tent was discontinued for this reason on May 18. The use of a steam tent, atropine sulphate, and ephedrine and amytal was started. The baby showed a decided improvement until May 21, when he seemed to fight more vigorously



Fig 1—Photograph of gross specimen showing group of caseous tuberculous lymph nodes deviating the trachea to the left and constricting the lumen of the left main bronchus. Millary tubercles may be seen through the pleura of the left lung.

for breath. Practically no breath sounds were coming through the left chest. The heart rate became gradually slower in spite of stimulants, and the baby died on May 22, nine days following admission to the hospital. Symptoms appeared to remain of an obstructive nature throughout. There was no evidence of meningeal or cerebral involvement at any time.

Necropsy Report—Necropsy was performed by Dr. Warren C. Hunter. Only the pertinent findings are recorded.

There were no pleural adhesions or exudate. The anterior margins of the lungs were blunt and emphysematous, and in the middle lobe of the right lung was an area of bullous emphysema measuring 2.0 cm by 0.7 cm. Near the base of the lower lobe anteriorly was an area 2.5 cm in diameter, where the pleura was raised up by closely set and confluent grayish yellow tubercles. These were directly continuous with other tubercles deeper in the lung substance. Over the posterior aspect of the lower lobe, beginning at the interlobar fissure and extending inferiorly, was a solid yellowish, slightly raised area, which extended down into the parenchyma.

for a distance of 1.5 cm. Grossly, this had the appearance of caseous pneumonia. In addition, there were quite a number of typical solitary miliary tubercles under the pleura on the posterior aspects of both lungs. There were no farther visible tubercles in the left lung. The parenchyma of each lung, where not tuberculous, was exceedingly bloody and exuded a frothy fluid on pressure. The trachea was deviated quite perceptibly to the left, the larynx being 1.2 cm. to the left of a line drawn through the carina. The displacement was accounted for by the presence of a firm mass situated along the right border of the trachea, beginning at the bifurcation and extending upward for a distance of 2.3 cm. The mass was firm on palpation, and when sectioned, proved to be made up of a number of large lymph nodes which had become fused into one mass and were at the time somewhat indistinct. All had yellowish, caseous centers. This group of nodes lay posterior to the thymus and was entirely separate from it. In addition to compressing and deviating the trachea, the tuberculous mediastinal nodes had pressed upon the right common carotid artery and made its lumen oval shaped. The thymus was not above average size for a child of this age. At the bifurcation of the trachea was another mass 2.0 cm. in diameter. This had a fibrous capsule and a yellowish caseous center. It had produced quite marked flattening and narrowing of the left main bronchus but had not affected the right.

With the exception of the right atrium the cardiac chambers were contracted. There was no evidence of tuberculous pericarditis.

On the inferior surface of the liver and under the capsule of the spleen were a number of translucent miliary tubercles, and in the parenchyma of the latter were some caseous lesions.

Microscopic Findings.—Sections of the mediastinal lymph glands and right lung showed extensive tuberculosis. In these locations, the inflammatory response was partly proliferative and partly exudative. Elsewhere, namely in the left lung, spleen, and liver the tubercles were of typical proliferative form, often with beginning caseation. The location of the lesions in the spleen and liver showed plainly their hematogenous origin.

Pathologic Diagnosis.—1 Focal caseous tuberculous pneumonia of the right lung

2. Caseous tuberculous mediastinal and tracheobronchial lymphadenitis with tracheal and bronchial compression and deviation of the trachea to the left

3 Hematogenous miliary tuberculosis of the liver and spleen.

SUMMARY AND COMMENT

The case history and necropsy report on a two month old infant are presented. The clinical course of an illness indicated tracheobronchial obstruction. The fact that there was no known source of tuberculous contact leaves room for speculation. During the clinical course there were no findings which definitely suggested a tuberculous origin of the disorder. Necropsy findings explained the obstructive symptoms. From the extent of the lesions, it appears unusual to us that there were no more clinical manifestations of tuberculosis. The anemia may have been due to the rapidly progressing tuberculous process. The pathologic lesions were more advanced than one would expect in a two-month-old infant.

THE TUBERCULIN PATCH TEST

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THE tuberculin patch test, carried out by applying to the unbroken skin a drop of undiluted old tuberculin, covering this drop with a patch of adhesive tape, and allowing it to remain in contact with the skin for forty-eight hours or longer, has been reported as a useful variation of the usual intradermal injection. Grozin¹ found an almost complete agreement in readings of the two tests. Wolff,² using tuberculin ointment, found 95.8 per cent agreement of tests performed with this material and Mantoux tests in which 0.1 mg. of old tuberculin was used.

Grozin pointed out that use of the contact test avoids the troublesome features of the preparation and administration of fresh tuberculin dilutions and eliminates the possibility of general systemic reaction and local necrosis. The last consideration is particularly applicable to negro children, in whom troublesome local reactions are rather common in our experience.

A group of patients were tested simultaneously with undiluted old tuberculin* by contact and 0.1 mg. of old tuberculin by intradermal injection. The results indicate that in cases in which the Mantoux is definitely positive, the contact test runs nearly parallel. The disagreement appears in those cases in which the Mantoux has been only slightly positive (one plus). Granting the difficulty of an accurate Mantoux reading in such cases, especially in the negroes, one must still attach sufficient importance to these slight intradermal reactions to lean toward the superiority of the intradermal method for general use.

Table I gives the groups on which the tests were made.

TABLE I

	TESTS AGREED			TESTS DISAGREED			PERCENTAGE OF AGREEMENT
	WHITE	COLORED	TOTAL	WHITE	COLORED	TOTAL	
1 Children under 2 years old	9	29	38	0	0	0	100.0
2 Children 2 to 14 years old	9	87	96	0	20	20	82.8
3 Adults	14	7	21	4	3	7	75.0
			155			27	85.2

From the clinics of the Charleston County Tuberculosis Association

*The tuberculin used was obtained from George C. Hulpritt, Saranac. The skin was cleansed with acetone, which was allowed to evaporate thoroughly, and the tuberculin was placed on the skin with a glass rod. The drop was then covered with a square of adhesive tape of good quality (Drybak) and left in place for forty-eight hours.

Among these groups there were 107 positive and 75 negative intradermal tests

There were twenty seven instances in which the tests failed to agree, but in twenty three of these instances the Mantoux reactions were only one plus, in two instances, two plus, and in only two instances were they four plus. In no case was the contact test positive when the Mantoux was negative. The Mantoux readings were made more on the basis of induration of the skin than on redness, for in some of the darker skins the difficulty of recognizing erythema was considerable.

Nine negro school children with positive Mantoux reactions and negative patch tests were given second patch tests, of which six were definitely positive and three negative. The reason for this change in response was not clear, unless the children had tampered with the adhesive tape in the original tests. Because the tape was removed by the children or otherwise loosened, it was necessary to discard a number of readings. The likelihood of such an occurrence is a real objection to the use of patch testing for groups of school children or other persons likely to remove the tape.

CONCLUSION

The tuberculin patch test seems to run in rather close agreement with strongly positive intradermal tests but is not comparable with the milder intradermal reactions. While the test presents some advantages over the Mantoux test, certain practical difficulties would seem to discourage its general substitution for the intradermal method.

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EXOPHTHALMIC GOITER BEFORE ONE YEAR OF AGE

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EXOPHTHALMIC goiter in preadolescence is uncommon, in childhood before five years, very unusual, and before one year, a real medical rarity

White¹ in 1912 reported exophthalmic goiter in a newborn infant, Klaus² in 1914, in a nine month infant, Helmholz³ in 1926, in a child of eleven months. These three, plus one to be presented here, give a total of only four such cases predating one year of age which we have been able to find in the literature. The three first mentioned above are included in McGraw's⁴ total of 157 preadolescent cases collected in 1928.

Because of its rarity the diagnosis of exophthalmic goiter in early childhood is quite frequently missed, and, even if diagnosed, the most effective line of therapy is much less well established than with the usual adult case. So to further, if possible, the total of medical and surgical experience in this condition, the following case is reported.

On Feb 7, 1933, a little girl, aged two and one half years, was brought by her mother to the Endocrine Clinic of the Children's Hospital of the East Bay, Oakland, Calif, with the complaints of nervousness, loss of weight, palpitation, and prominence of eyes.

She had been a seven month, premature infant, weighing $4\frac{1}{2}$ pounds, delivered normally. She was born in Utah, but the family had left there two months later and had lived in Oakland since. She was breast fed until she was three months old. At six months her eyes were definitely more prominent than normal. By nine months she was noticed to be unusually irritable, and attacks of vomiting and diarrhea began to recur. At one year of age she had a convulsion, and the examining doctor told the parents the child had a "bad" heart, its rate being far too rapid. Any excitement produced marked palpitation. About this time, too, the parents first noticed the swelling in her neck but did not consult any physician regarding it.

While she had been slender since the age of one year, her weight gains had been very good till the previous six or nine months, when she had actually lost 4 or 5 pounds. Her appetite had always been poor, especially for vegetables and meats, though she consumed generally about one and one-half quarts of milk daily. Her bowels had always been very irregular with alternating constipation and diarrhea, the latter generally associated with some vomiting. She had had three convulsive seizures during the past eight months. These lasted from two to three minutes and consisted of unconsciousness, twitching, and cyanosis without incontinence.

During the six months prior to her first visit to the clinic, the child had been much more irritable and nervous. Her eyes had become increasingly prominent during the last three weeks, and some tremor of her hands had been noted the last week or so. Her sleep had become quite fitful.

Her hair had always been scanty and fine. She perspired freely and easily. She passed through measles and mumps uneventfully at two years.

The patient's mother was seventeen years of age at the time of the patient's birth. She had a "goiter" while in school which disappeared when iodine pills were taken. Thus, according to her history, was symptomless. While pregnant with this patient, a moderate return of her goiter occurred without symptoms.

The father of the patient, two years older than his wife, was perfectly well. His grandmother's sister had had a goiter. The patient had one brother aged one year apparently normal in every respect.

Following are my initial physical findings when the patient was referred by the clinic to the Children's Hospital on Feb. 7, 1933.

The patient was a fairly well-developed, poorly nourished child, apprehensive but cooperating well. Scalp was oily, hair fine in texture. Ears were negative.

The pupils were round and equal, and reacted well to light and accommodation. Extraocular movements, normal. There was marked exophthalmos, no definite lid lag or inability to converge, no strabismus or nystagmus.

The nose was dry, with slight congestion. Teeth were normal, mucous membrane, throat and tonsils, negative. There was no stiffness of the neck, slight postcervical adenitis.

The thyroid was diffusely enlarged (both lobes and isthmus), especially the right lobe which ran well up to the hyoid bone. No nodules were felt. There were thrills over both lobes, loud murmurs were heard over whole. Gland did not seem to run below sternum.

Chest showed good symmetrical expansion with the lungs clear throughout. Heart point of maximum impulse within nipple. Left cardiac border slightly beyond nipple line. The rate was regular, 168 per minute.

Blood pressure (lying) was 140/60. Systolic blow was heard over the whole precordium transmitted to the neck. Diastolic murmur was heard at times, no axillary transmission. Pulmonic second sound louder than aortic second.

The abdomen was scaphoid, no solid organs were felt, no tenderness or rigidity. The genitals were those of a normal female infant.

In the extremities a fine tremor was present on movement. The skin was warm and moist. Reflexes were normal and active.

A diagnosis of exophthalmic type of hyperthyroidism was made.

Laboratory findings were: R. B. C. 5,260,000; hemoglobin 14.5 gm; W. B. C., 5,500; polymorphs 41 per cent; S. L., 20 per cent; L. L., 22 per cent; monocytes, 6 per cent; lymphoblasts 2 per cent; urine negative; O. T. 0.1 mg; I. D. (H. & B.) negative.

Sugar tolerance, fasting 78 mg per cent; peak of 100 at one hour, 88 at two hours, no glycosuria during test. Blood Wassermann was negative.

X-ray examination showed no evidence of tracheal displacement or compression. Thymus was normal. The sella was within normal limits, and there were no shadows suggesting suprarenal tumors.

During an initial period for the purpose of observation and further study she was allowed a high calorie diet and no medication except small doses of phenobarbital (gr $\frac{1}{4}$ t.i.d.). Her temperature varied from 101 to 99 F (all temperatures rectal) and her pulse rate from 184 to 120.

On the sixth day her temperature rapidly rose to 106 F and her pulse, to 160. She vomited, and her stools became quite loose. Nervousness increased. Her voice became much more husky than usual and she pulled at her neck as though there was a sensation of pressure or tightness there. Her nose began to run, her throat became moderately injected and her lungs full of fine moist rales. Plainly a crisis had occurred precipitated by the respiratory infection.

Ephedrine drops were used intranasally, 10 per cent glucose was given intravenously, and sedation was increased. Her fever was ineffectually treated by continuous colonic flushes and cold packs. Since Lugol's solution could not be retained by mouth or rectum, intravenous sodium iodide (2 c.c. of 10 per cent solution) was given for three days.

On the tenth day a generalized "Inmmal" rash appeared, necessitated the discontinuance of barbiturates, sedation was secured henceforth largely by codeine and bromides. By the thirteenth day her temperature had returned to normal and her pulse, to 120. She was then taking 15 gr. of potassium iodide daily by mouth. Her weight had dropped from 27 pounds to 24½ pounds.

The iodide was increased to 20 gr. daily. Her pulse rate dropped gradually to a low of 88 on the eighteenth day. On the nineteenth and twentieth days basal metabolism tests were made. The little patient cooperated well, the rates being plus 21 and plus 23, according to Benedict's tables calculated on height. Her weight at this time was 25 pounds, 5 ounces, and blood pressure, 110/60.

Joint surgical, x ray, and medical consultation was of the opinion that it would be wiser to follow a conservative course and employ x ray therapy at this time rather than surgery. The iodide was gradually cut to 1 gr. daily, and three moderately heavy x ray treatments were given at weekly intervals.

By the time she had received her third x ray exposure, although her weight had increased to 27 pounds and she looked very well, she was markedly more nervous and emotionally unstable. Her pulse had gradually risen to 160 to 170. Her bowels became loose, and attempts at metabolic readings were exceedingly difficult, readings of plus 163 and plus 165 being obtained on two successive days. Her thyroid was much firmer and definitely nodular.

It was then decided to drop the idea of x ray therapy, to begin intensive iodine medication again with the expectation of employing surgery if we could put her into proper condition a second time. Lugol's solution was given, the daily dose being gradually increased to 45 minims. Despite this and sodium bromide, 10 gr. every four hours, her pulse would not drop lower than 130. Basal metabolism readings were inaccurate because of her poor cooperation.

After three weeks of intensive iodine medication, when it was seen further improvement was unlikely, bilateral superior pole ligation was performed under nitrous oxide anesthesia by Dr. Dexter N. Richards. The operative report was as follows:

Bilateral incisions were made over both superior poles. The larger lobe was on the right. The vessels were larger there, and thus pole extended higher in neck, making vessels more mesial. They were doubly ligated with No. 1 chromic catgut. On the left, the pyramidal lobe was first brought into view, a portion being removed for examination. The left superior pole and vessels were then exposed and vessels again doubly tied with chromic catgut. Subcutaneous tissues were closed with fine plain catgut and skin clips.

Dr. Paul Michael examined the section obtained at operation and reported: "Microscopic sections show portions of thyroid gland in an active state of hyperplasia. There is a small amount of colloid material, probably stored recently due to new growth, and a small amount of excessive fibrosis in the stroma. The essential change observed consists of an adenomatous pattern. The acini are for the most part small and lined by a high cuboidal or high columnar epithelium, resting on a basement membrane which is preserved and giving evidence of marked infolding or feathering. The vessels of the gland are moderately engorged. Diagnosis: hyperplasia of the thyroid gland—very mild involutional changes."

Her postoperative reaction was moderately severe, her temperature going to 103.8° F., and pulse, to 180, with some vomiting and diarrhea which was easily

controlled and soon stopped. She was kept on Lugol's solution 5 minims t.i.d., and sodium bromide, 5 gr t.i.d. Her pulse stayed between 120 and 130, and she was much quieter. Yet despite this and a fair appetite her weight decreased to 24 pounds 14 ounces on the fourteenth day postoperatively.

On the twentieth day another acute respiratory infection developed with a second crisis, her temperature rising to 105 and 106 F for three days with marked increase in nervous symptoms and transient delirium. Following this the Lugol solution was gradually increased to 18 minims t.i.d., her pulse rate still averaging about 130. Coincident with 5 minims of insulin a.c., and the daily quartz light treatments, her weight increased to 27 pounds 12 ounces.

Forty days after her first operation her basal metabolic rate was plus 54. Dr Richards then performed a right subtotal lobectomy under nitrous oxide and local anæsthesia. "Two ounces of $\frac{1}{2}$ per cent novocaine without adrenalin injected for a Kocher type incision, placed a little higher than usual. The usual approach to the

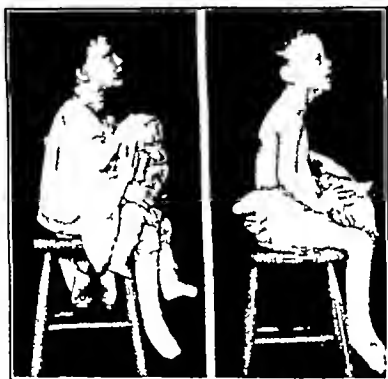


Fig. 1.

Fig. 2.

Fig. 1.—Photograph taken on twenty-fifth day when patient was in her primary iodine remission, with a B. M. R. of plus 22 and pulse of 80. X-ray therapy was begun at this time.

Fig. 2.—Photograph taken the day before her thyroidectomy 40 days after the pole ligation. B. M. R. plus 54, pulse, 130. Gland was much firmer and smaller but patient was much less cooperative and quiet than when first pictures were taken.

gland without cutting muscles was used. The gland was easily delivered, and there was no excessive bleeding, nor were there any adhesions that could be attributed to x-ray treatment. The gland was much paler than at previous operations, and the superior pole was almost white as a result of the previous ligation. A right subtotal (4/5) lobectomy was performed, bleeding points tied and muscles very loosely tacked together over a penrose tube drain. The skin was closed with clips; no attempt was made to close the platysma. Her condition was satisfactory all through the operation."

Dr Paul Michael's pathologic report is as follows:

Gross Findings.—The specimens presented a firm smooth surface. Cut section showed a meaty type of gland presenting marked cellularity and vascularity. There was some increase in fibrous tissue noted.

Ephedrine drops were used intranasally, 10 per cent glucose was given intravenously, and sedation was increased. Her fever was ineffectually treated by continuous colonic flushes and cold packs. Since Lugol's solution could not be retained by mouth or rectum, intravenous sodium iodide (2 c.c. of 10 per cent solution) was given for three days.

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Opinion as to the right amount of gland to be removed varies greatly although the trend seems to be toward removing an amount comparable to that removed in the adult—more than was formerly advocated

McGraw⁴ states "While we doubt that polar ligation of the superior thyroid arteries is a sufficiently radical procedure to insure permanent recession of symptoms, we feel that one should be a shade more conservative in the relative amounts of thyroid tissue left behind at operation as compared with that left in cases of adult exophthalmic goiter even risking the necessity of subsequent reoperation, until we have some accurate data on the effect of subtotal thyroidectomy upon human growth and development." Similarly, Means and Richardson⁵ write "Treatment of exophthalmic goiter in children, on account of the milder course permissibly may be more conservative than in adults. As we noted earlier, the symptoms are less marked and the course more definitely self limited. Subtotal thyroidectomy, therefore probably will rarely be necessary, and there are certain obvious reasons why it is less desirable to deprive a growing child of five sixths of his thyroid than an adult. X ray would seem to be the method of choice with thyroidectomy only in cases that did not show a satisfactory improvement after a reasonable length of time (three or four months)."

On the other hand Beilby and Carleton⁶ state "Experience may teach us that thyroid tissue regenerates more rapidly in the young individual and that we can safely remove an amount at least proportionate to the older patient."

Crile⁷ expresses the opinion that "the younger patient requires the removal of more than the older one—the larger the gland the more mass is left."

The results obtained in the case here presented, i. e., mild hypothyroidism following a hemi-subtotal thyroidectomy, may be explained as the result of the additional repression of gland activity caused by the preoperative x ray therapy and the superior pole ligation.

One well-established statement is amply verified by this case "Employ iodine to obtain a remission of symptoms and that only preoperatively." Hope that the iodine remission will persist and further treatment be unnecessary is like hiding in one's straw house to avoid the wolf.

SUMMARY

A case is presented of a two-and-one half year-old child with severe exophthalmic goiter whose symptoms began when she was six months old. The benefits of an iodine remission were lost (and never completely regained) in order to employ x ray instead of surgery. When this failed to halt the progress of the condition, bilateral superior pole ligation was performed and later hemi subtotal ($\frac{1}{2}$) thyroidectomy. Mild hypothyroidism resulted.

NOTE A child of a subsequent pregnancy of the patient's mother is said to show symptoms similar to the sister reported here

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CLINICAL RECORD AND POSTMORTEM PATHOLOGY OF DIABETIC CHILDREN

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DIABETES in children is no longer a clinical curiosity. Further more, with the advent of insulin, the ranks of diabetic children in this country are swelling rapidly each year at the rate of about 1,000. On the whole, the progress of these children is good and it is better with each succeeding year of their diabetes. The first year of their diabetes is the critical year and highest mortality rate among diabetic children occurs during this time. This is not due to the fact that the inherent nature of diabetes is any different in the first year than in the later years, but rather to the fact that the mother and the family doctor are facing a problem which is new to them. They either learn to handle it reasonably well and meet adequately the complications which may occur, or else they fail in some way or other, and death is the result. The next two years of diabetes of a child are still fraught with danger, owing to the same factors. After three years the accidents happen less frequently, as by that time the mother has learned her problem well, and she is accustomed to meeting the various emergencies as they arise.

Thus among 214 diabetic children under my care (from one to twenty years of age) the mortality during the first year of diabetes was 39.2 per cent of the total mortality which was 13 per cent¹ this includes two years in the preinsulin era, and the deaths among patients who had diabetes for three years or less constituted 64.2 per cent, of the total number of fatalities. These figures show that it behooves us to exert a special effort the first year in every new case of diabetes in a child and to maintain close supervision during this time. Accidents will always occur but they are apt to be much more frequent at the beginning.

Diabetes can occur at any time of a child's life. In Table I, I have charted cases gleaned from the literature. All seventy-eight of these patients are under one year of age. There are six cases of congenital diabetes and four more which were discovered within a few days after birth and could thus be classified as congenital. This speaks strongly for heredity for at this age other factors can certainly be ruled out. Heredity is an important factor in the etiology of diabetes in children. Thus among my own group of Jewish children, there was a familial history of diabetes in 30 per cent, in Joslin's series in 44 per cent and in Priesel Wagner's in 43 per cent. In the non-Jewish children heredity

was a factor in my own cases in 17.9 per cent and in Priesel Wagner's cases in 21 per cent. This means an increase in the heredity factor in the Jewish group of 101 per cent.

Infection seems to stand next in line as an etiologic factor. This is by no means a new idea, for acute infections as the cause of some cases of diabetes was suggested first by Aretaeus of Cappadocia² (A.D. 30 to 90) who lived under the Emperor Nero. I have reported³ eleven children in whom the onset of diabetes was within the first ten days after various infections (some as early as second and third day), seven in whom the onset of diabetes was from eleven to twenty days after, and thirteen, from twenty-one to thirty days after. I have gathered from the literature ninety-eight cases (including my own) in which the diabetes followed infectious diseases. The possibility of diabetes developing after acute infectious diseases must be kept constantly in mind and for three to five weeks following any infectious disease, the physician should be on the lookout for glycosuria. The whole problem of the treatment of diabetes hinges upon its early discovery, before too much damage has been wrought to the pancreas.

Over a period of fourteen years, 1920 to 1934, a period which goes back two years into the preinsulin era, I have had under my care 214 diabetic children between the ages of one and twenty years. Of these, 186, or 87 per cent are living and twenty-eight, or 13 per cent are dead. An analysis of the twenty-eight cases in which death occurred is given in Table II.

Of this group four came to autopsy, and I am recording these cases in detail in this communication. In one case adrenal denervation had been performed and the patient died of adrenal insufficiency at the age of twenty-one years, having had diabetes less than one year. The diabetes had been secondary to hyperthyroidism. One patient died in coma at the age of ten years, having had diabetes for six years. One patient had acute bilateral pulmonary tuberculosis and died at the age of twenty-one having had diabetes for six years. One girl, aged sixteen years, who had diabetes for eight years, died in coma and had fatty degeneration of the liver. She was first seen *in extremis* and died within an hour after her arrival.

Allen's dictum, "Without pancreatitis there is no diabetes," seems to hold when one studies the pathologic reports in the literature. Some cases are reported in which no changes in the islands were found, but these represent largely pathologic studies in which special staining methods had not been employed. Consequently, we must take this fact into consideration. Even in the presence of negative findings a functional change in the islands is not ruled out, a fact which Allen pointed out many years ago. The closer one studies any problem the more evidence he finds. This dictum can be applied to the pathologic study of diabetes.

TABLE II

MORTALITY OF 28 CHILDREN IN A SERIES OF 214 DIABETIC CHILDREN *

NO	AGE IN YEARS		SEX		CAUSE OF DEATH								DURATION OF DIABETES IN YEARS
	ONSET	DEATH	M	F	COMA	TUBERCULOSIS	ADRENAL DENERVATION	KILLED IN ACCIDENT	APPENDECTOMY	SEPTICEMIA	OTITIS MEDIA	UREMIC COMA	
1	16	19	o		o								30
2	18	23	o		o								50
3	20	21	o				o Pm.						10
4	14	18	o										40
5	14	14	o		o				o				01
6	11	11	o		o								01
7	4	10	o										60
8	17	23		o	o								60
9	14	16	o		o								20
10	7	7	o		o								01
11	5	7	o		o								20
12	1	1	o		o								03
13	5	6	o		o			o					10
14	10	11	o		o								10
15	7	11	o		o				o				40
16	12	12	o		o								05
17	4	10	o		o Pm.								60
18	12	13	o		o								10
19	4	11	o							o			70
20	19	20		o	o								10
21	3	4		o	o								10
22	15	21		o		o Pm							60
23	18	18		o							o		05
24	8	16		o	o Pm.								80
25	17	17		o	o								00
26	14	15		o	o								10
27	12	20		o		o							80
28	18	18		o								o	02
Total			18	10	18	3	1	1	2	1	1	1	

Total deaths 28 Of these I took care of 5 Cause of death of these Case 3, adrenal insufficiency after denervation, Case 5, coma, preinsulin era, Case 6, coma, preinsulin era, brought in last stage, Case 24, coma, brought in last stage, Case 25, coma, died one hour after reaching hospital.

*Includes preinsulin era ages one to twenty years

P m—Postmortem.

Note the frequent and varied changes in which Shields Warren⁴ finds in his pathologic studies in diabetes With all his reservation and his characteristic thoroughness the evidence which he brings out seems quite marked.

Table III presents the pathologic findings at postmortem of twenty-four children as reported in the literature by various authors In only two of these no changes in the pancreas were reported

In the study of the gross and the minute changes in autopsy specimens of the pancreas from persons other than diabetic patients, according to Keltz,⁵ many different pictures are encountered which are principally the loss of structure, true atrophy with fatty replacement, calcification,

TABLE III
AUTOPSY REPORTS ON DIABETIC CHILDREN

NO	AGE IN YR.	NO ISLANDS DIMINISHED	ISLANDS DIMINISHED IN SIZE	FIBROSIS, ATROPHY, SCLEROSIS OF PANCREAS	HYALINE DEGENER. OF ISLANDS	HYDROPIC DEGENER. OF ISLANDS	NECROSIS OF PANCREAS	CONGEN. ATROPHY OF PANCREAS	NO ISLANDS	NO CHANGE	AUTHOR
1	0.25	o									Heiberg
2	0.66	o									Kochmann
3	0.75	o	o								Knox
4	1.25	o									Heiberg
5	3.00			o	o	o					Martins
6	4.00						o				Anderson
7	4.50	o		o							Heiberg
8	4.50	o									Heiberg
9	5.00	o									Heiberg
10	5.00	o		o							Heiberg
11	6.00	o									Bihlmeyer
12	7.00			o							Phillip
13	10.00			o					o		John
14	11.00			o							Frontini
15	12.00			o	o	o					Martins
16	14.00							o			Ghon
17	15.00									o	Nobocourt
18	15.00			o	o	o					Martins
19	16.00		o	o							John
20	16.00			o	o	o					Martin
21	16.00			o							Lindblom
22	16.00	o		o							Lancereaux
23	20.00		o	o							John
24	21.00									o	John

passive congestion arteriosclerotic changes with perivascular fibrosis, interlobular intralobular, interacinar and intracinar fibrosis with hyalinization and lymphocytosis and variations in the size and number of cells of the islands of Langerhans. The island changes in non diabetics are not so marked or so striking as in the diabetics. In addition to these the pancreas is the seat of acute inflammation, specific inflammations, tuberculosis and syphilis and congenital deficiencies with cysts and neoplasms.

Opie⁶ sums up the work of R. L. Cecil, a study of ninety cases of diabetes as is shown in Table IV

In seventy nine cases or 88 per cent of the ninety cases of diabetes Cecil found lesions of the islands. Hydropic degeneration was not

TABLE IV

<i>Interacinar pancreatitis</i>	
With sclerosis of the islands of Langerhans	39
With hyaline degeneration of the islands of Langerhans	19
With sclerosis of the islands of Langerhans and lipomatosis	2
With hyaline degeneration of the islands of Langerhans and lipomatosis	1
With sclerosis of the islands of Langerhans and hemachromatosis	2
Total	63
<i>Interlobular pancreatitis</i>	
With sclerosis of islands of Langerhans	4
Total	4
<i>Parenchyma normal, lesions of islands of Langerhans</i>	
Sclerosis of islands of Langerhans	4
Hyaline degeneration of islands of Langerhans	7
Infiltration of leucocytes of islands of Langerhans	1
Total	12
<i>Pancreas normal in structure</i>	
Pancreas, small, and islands of Langerhans, few	2
Islands of Langerhans, few	3
No abnormality noted	6
Total	11

ruled out, as the refined methods of fixation and granular staining of Lane and Bensley were presumably not carried out in this series

Keilty states that in his experience the finding of a small pancreas, which presumably has a decreased number of islets, is the most common and striking finding in cases of diabetes. Whether this is congenital or a part of a general atrophic change, whether secondary or primary to diabetes, may be still open to argument.

Hoehn⁷ studied autopsy records of twenty one cases of diabetes and found island changes in all. Conroy⁸ studied twelve cases with serial blocks of tissue and showed a reduction of insular tissue of 50 per cent. Every case showed qualitative changes in the islands, hyalinization and fibrosis. These changes were not so noticeable in nondiabetic controls.

Allen⁹ reviewed a total of 570 cases in which the pancreas was studied. There were abnormalities in 48 per cent of the 549 individuals who were nondiabetic, he found abnormalities in 100 per cent in the twenty-one who were clinically diabetic.

TABLE V

COMPARATIVE PATHOLOGIC REPORTS IN ADULTS AND IN CHILDREN

	TOTAL CASES	NO CHANGE IN PANCREAS	PER CENT	DEFINITE CHANGE IN PANCREAS	PER CENT
Children	24	1	4	23	96
Adults	364	18	5	346	95

I have gathered from the literature a record of the microscopic examinations in 388 cases of diabetes. Of these, 364 were in adults and twenty four in children. Reports of the findings in these two groups are shown in Table V

CASE REPORTS

CASE 1—A young man, aged twenty years an automobile painter was admitted on the surgical service Oct 13 1930. He complained of loss of weight and nervousness polyuria and frequency. About six months before he had begun to lose weight. His endurance was poor, he felt tired and run down. About four weeks before he had begun to pass large amounts of urine and to drink large quantities of water. A diagnosis of diabetes had been made and he had stayed in a hospital for ten days with no improvement. After leaving the hospital, he noticed that he was becoming more nervous he developed a tremor of the hands and he perspired a great deal and felt drowsy most of the time. He had a voracious appetite. The family history was negative.

His weight at this time was 103 pounds height 5 feet 6 inches his best weight had been 140 pounds. His blood sugar content at this time was 200 mg per cent, four hours after eating. The blood urea content was 30 mg per cent. There was no sugar in the urine and but a faint trace of albumin. Physical examination was negative with the exception of the tremor of the hands. The basal metabolic rate was plus 20 per cent he presented the typical picture of hyperthyroidism. On small dosages of insulin the blood sugar fluctuated at a low level on a 3000 calorie diet (Chart 1). A few days later a glucose tolerance test revealed a frankly diabetic curve. After a short stay in the hospital he was sent home on the 3000 calorie diet and 5 units of insulin which had to be increased to a dosage of 4-0-4 then to 8-0-8 and finally to 15-0-15 units.

He returned in a little over a month during which time he had gained 12 pounds and was generally improved. His fasting blood sugar at this time was 120. A basal metabolic rate taken on the third day was plus 32 per cent the glucose tolerance test was repeated and gave the same type of curve as before. With the increased metabolism, the insulin requirement increased to 20-20-20 units per day. Lugol's solution was administered and gradually reduced the basal rate. The blood sugar level, in spite of the increase in insulin was considerably higher now. In two weeks denervation of the left adrenal was performed in an effort to control the hyperthyroidism and diabetes. Immediately following this for four days the level of the blood sugar rose. The insulin had to be increased to 15-15-15 units per day. Two weeks after the denervation the patient returned home, the insulin dosage being 15-15-15 units.

He returned to the hospital in three weeks. His blood sugar level at this time was higher fluctuating at about 230 mg per cent. The basal metabolic rate had risen to plus 43 per cent. On the third day after his return, the second adrenal gland was denervated on the second day following the operation he died. His death looked like that caused by thyroid crisis there were rales scattered throughout both lungs. Tracheotomy was performed, and an oxygen tent used, without improvement of symptoms.

The postmortem examination cleared up the complex clinical picture. The first adrenal was fibrosed the gland atrophied—thus not functioning. The second adrenal showed multiple thrombi in the vessels the medulla was hemorrhagic, thus also not functioning. The man died of acute adrenal insufficiency.

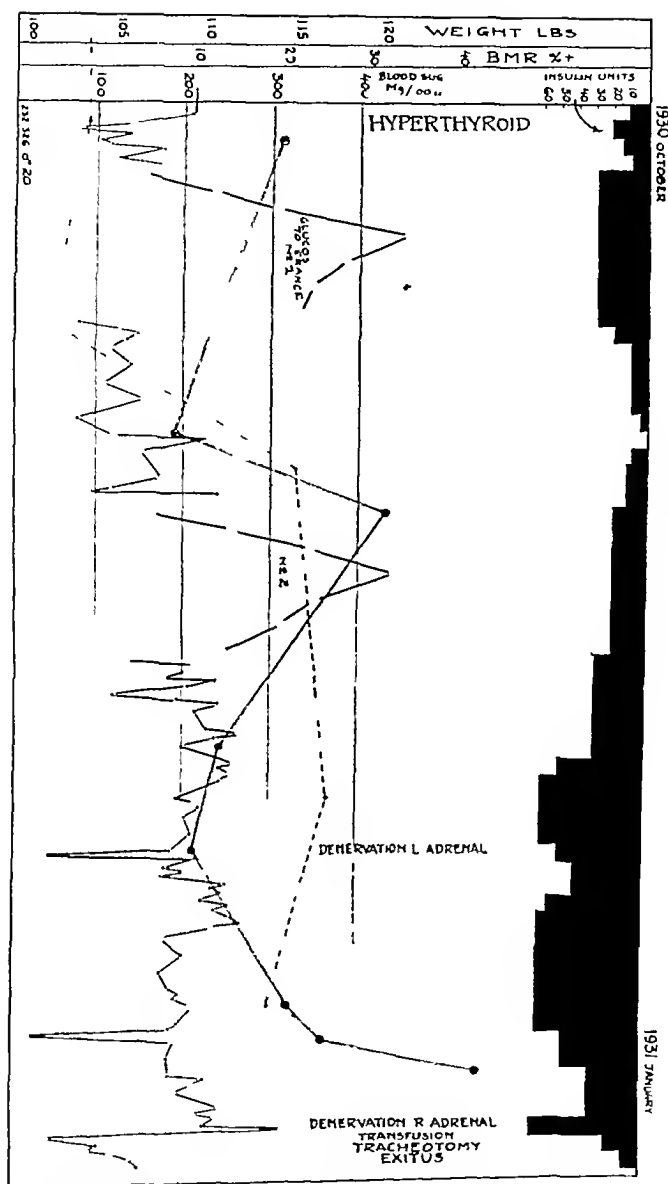


Chart 1—Progress in Case 1 Youth twenty years old with diabetes and hyperthyroidism died of acute adrenal insufficiency following bilateral adrenal denervation.

Pathologic Report

Adrenals—The right adrenal was imbedded in a large quantity of formed adhesions and fibrofatty tissue. It was large and on section showed, in the lower pole, multiple thrombi in the vessels. The cortex was apparently intact, but the medulla was quite hemorrhagic and in several areas contained a large amount of old, clotted blood. There was poor differentiation between cortex and medulla, and in one area cloudiness suggesting early necrosis.

The left adrenal was imbedded in a mass of white, old scars. A portion of the gland was atrophied. There was very little substance remaining, either cortical or medullary. The portion, however, that did remain showed fair differentiation.

Sections of right adrenal showed extensive, recent hemorrhage, thrombosis of vessels and necrosis of adrenal tissue. There were only a few, relatively small areas of comparatively normal cortical tissue present. The surrounding fat contained a large amount of blood, fibrin, and leucocytes.

Sections of the left adrenal showed fairly large areas of comparatively normal medullary tissue and scattered areas of somewhat altered cortical tissue. The capsule of the adrenal and surrounding tissues showed great increase of fairly dense, collagenous fibrous tissue in which were many lymphocytes, plasma cells, and a few leucocytes and phagocytes containing blood pigment. A large artery apparently belonging to the adrenal, showed obliterating endarteritis. There was a large sympathetic ganglion in the section and a small hyperplastic lymph node.

Another section of this adrenal, probably at the opposite end, showed large areas of necrosis and degeneration of a greater portion of the cortical tissue, with only a small area of comparatively well preserved cortex near one end. There was extensive fibrosis in and around the adrenal.

Thyroid—The thyroid weighed 50 gm. Both lobes were slightly enlarged. The left superior and right inferior parathyroids were present. Section of each lobe showed a slightly hyperplastic gland with a great amount of lymphoid. It was present in large and small, discrete areas. There was considerable colloid there were no adenomas.

Sections showed goiter hyperplastic, moderate (involuting) with very little increase of stroma, no lymphoid tissue, and no adenomas. One section showed a normal parathyroid.

Thymus—The thymus weighed 50 gm. It measured $18 \times 6 \times 2$ cm and was greatly enlarged made up of two lobes. It was soft, white, and fairly friable. Sections of the two lobes showed a white, glandular structure with fibrous tissue trabeculae.

Section showed hyperplastic lymphoid tissue with numerous small and large Hassall's corpuscles, some of which apparently were undergoing a granular or hyaline degeneration.

Liver—The liver weighed 1,380 gm. The right lobe measured $18 \times 20 \times 9$ cm., and the left lobe $8 \times 17 \times 6$ cm. The contour was normal the edge was fairly sharp and the capsule stripped readily. The vena cava and portal veins were clear. Section of liver showed fairly distinct lobules. The central veins were prominent and patent. Several of the smaller hepatic arteries showed a cloudy, milky chylelike substance. There was bile present in several of the smaller bile ducts. The cut section had a rather cloudy homogeneous appearance. There were no definite tumor nodules and no evidence of focal necrosis.

Sections of the liver showed congestion of vessels, no increase of fibrous tissue. The liver lobules and cords were practically normal except for numerous, small vacuoles in a large number of liver cells in many lobules, probably fat. In addition there were localized areas of larger fat globules in various sections. The biliary ducts appeared normal.

Pancreas—The pancreas weighed 90 gm. and measured 17 cm. in length. At the head it measured 5×3 cm., and at the tail, 3.5×2.5 cm. Cut section showed no gross abnormality. There was no fibrous or fatty infiltration of any portion.

The microscopic examination showed a definite increase of interlobular fibrous tissue and increased fibrous tissue around the blood vessels and the larger pancreatic ducts. There was very little fat in the pancreas. The lobules generally were well

preserved The islet tissue, generally, was inconspicuous In some sections, particularly in the region of the head, there were a few normal sized and larger histologically normal islands A few islands showed a moderate degree of atrophy and fibrosis, and an occasional lobule showed atrophy and fibrosis

CASE 2—The patient, a boy, who was ten years old in 1930 when first seen, had had diabetes for six years Diabetes had appeared a few days after an infection, whooping cough and Vincent's angina. He was on a special diet and was taking 25 units of insulin once a day He had been in coma several times and had had measles and chickenpox during the course of the diabetes He also had had a mastoid operation three years before Briefly, his condition was not well con-

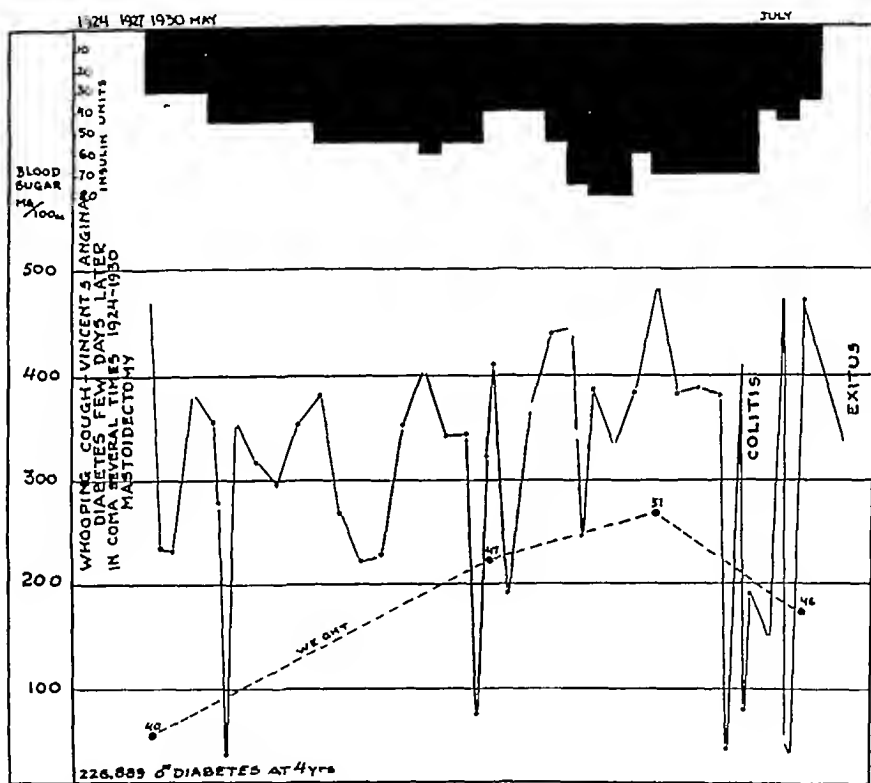


Chart 2—Progress in Case 2 Boy developed diabetes at the age of four years following a severe throat infection and died six years later in coma following another infection colitis

trolled, and he was gradually becoming more severely diabetic Inquiries concerning the family history elicited the fact that a maternal aunt and two cousins had diabetes

When he was first seen, May 22, 1930, his blood sugar content was 476 (Chart 2), he had pronounced glycosuria He was given an 1,800 calorie diet and 10 10 10 units of insulin, this dosage being increased to 15 15 15 and then to 15 15 15 15 His diet, because of his undernutrition, was raised to 2,500 calories, and marked gain in weight resulted The figures in Chart 2 represent fasting blood sugar contents, thus high in values, his twenty four hour sugar output at the beginning was fluctuating from 5 to 50 gm He was discharged from the hospital in five weeks, on a 2,000 calorie diet and 20 10 10 10 units of insulin

Ten days later he developed fever and diarrhea followed by acidosis. As he lived in a small town without facilities for hospital care he died on the fourth day.

This child had had severe diabetes for six years and had lost much of his sugar tolerance. His blood sugar was high and the insulin could not be raised above the amounts mentioned because he suffered severe insulin reactions. He was losing on the average, about 20 gm of sugar per day and getting from 100 to 120 gm of carbohydrate. A diabetic child who has a severe type of diabetes is always a difficult problem, especially if infections occur for there is little to fall back on. Acidosis develops quickly, liver glycogen reserves are small or nonexistent thus coma follows quickly the onset of acidosis. If there is much delay in getting such a child to a hospital, death occurs in a short time, as in this case. Though this boy was ten years old, his stature was that of a six year old. He gained much weight and improved in every way during the five weeks of his hospital stay yet the type of response seen usually in a child in the early stages of diabetes was lacking. A patient of this type requires much insulin and while one reaches finally a state of equilibrium such a state remains stationary with little or no increase of tolerance with time. In other words, in such a late state of diabetes, the damage done is permanent, and the process is irreversible.

The postmortem examination showed a small soft pinkish gray spleen. Both kidneys showed an adherent capsule and little congestion in the cortex. The liver was small soft, pale red and cut with little resistance the cut surface was beefy red bleeding moderately. The spleen was unusually large. The pancreas was small and firm. The gallbladder was somewhat enlarged, adherent to the under surface of the liver—ducts patent. The heart was of average size. The thymus was not enlarged.

The microscopic examination was as follows. The glomeruli of the kidneys were unusually large their capillaries packed with red cells. Renal tubules especially their proximal portion, were lined with swollen and cloudy cells. Some were filled with hyaline material. There was marked increase in the interstitial connective tissue. The blood vessels were distinctly thickened and fibrous.

The pancreas showed marked perilobular fibrosis. The small blood vessels exhibited marked fibrosis and thickening. No recognizable islands of Langerhans could be found.

Adrenals showed marked autolysis considerable deposits of pigment, and red cells the spleen was markedly congested.

CASE 3—A girl sixteen years of age when seen first in 1926 nine months after diabetes had developed following influenza and pneumonia. Here was a typical case of fully developed, uncontrolled diabetes. The patient's weight had dropped from 115 to 86 pounds in six months. She was very nervous and suffered from nocturia, thirst, marked polyphagia and bloating of the stomach. She had been told she had appendicitis and ovarian trouble.

While her diabetes according to the history developed in January it was not diagnosed until June when she had the symptoms mentioned. Following the influenza the family physician gave her an increased diet in an effort to help her regain her losing weight and strength. Even after the diagnosis of diabetes was made six months later, she was given no insulin and she did not pay much attention to her diet.

When I saw her on Oct. 6 1926 (Chart 3) she presented the typical picture of an emaciated diabetic youngster. She had a blood sugar content of 337 acetoneuria and lipemia. The urine contained 33 per cent sugar heavy acetone, and diacetic acid. The plasma carbon dioxide was 23.3 mm.

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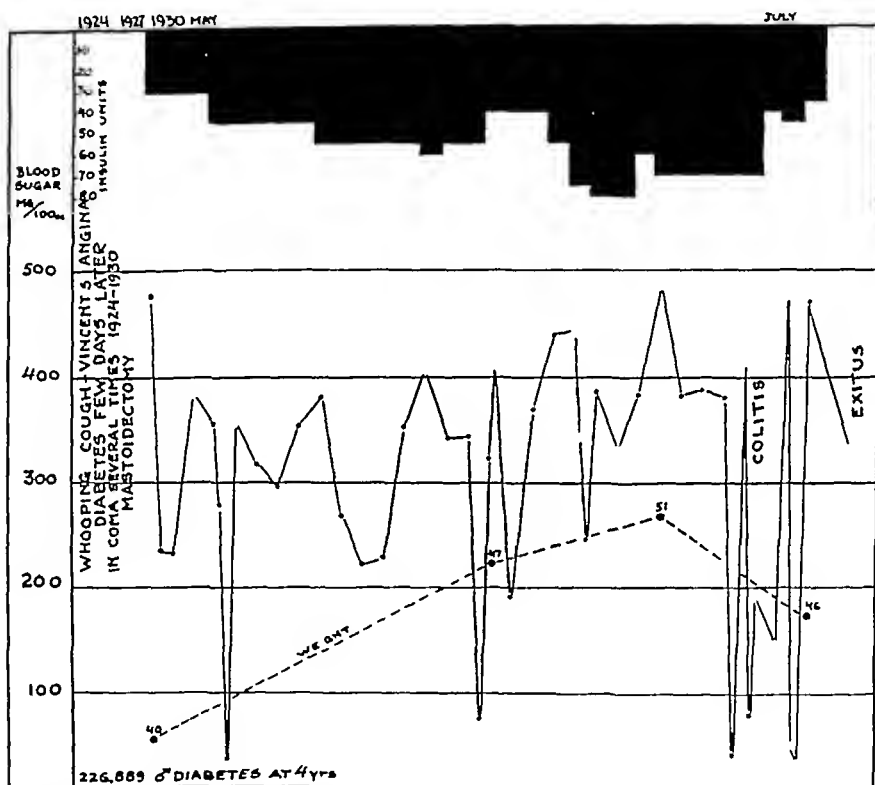


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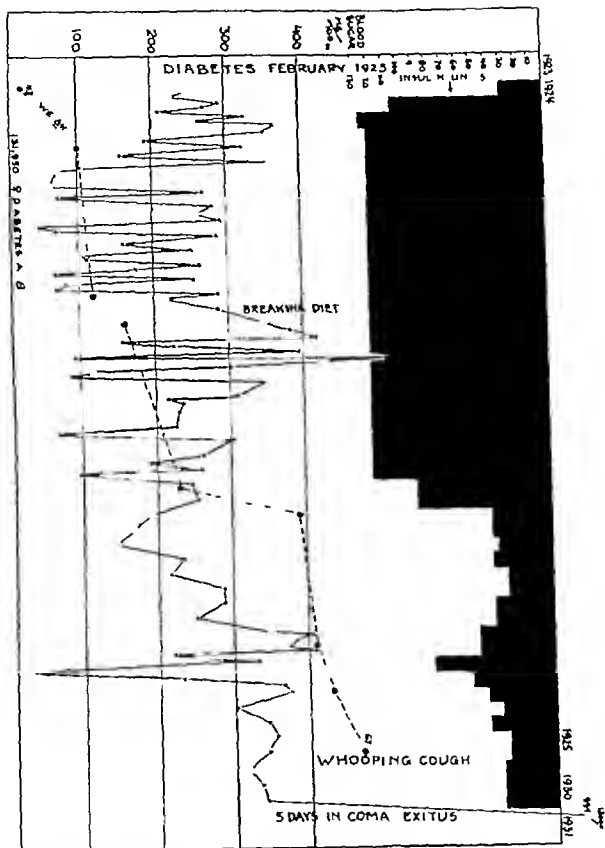


Chart 4.—Progress in Case 4. Girl developed diabetes at the age of eight years and died eight years later in coma due to the discontinuation of insulin. This child had a large fatty liver

married. Pregnancy soon followed. During the latter part of her pregnancy her diabetic condition improved considerably. Had it not been for the intervening infection which necessitated temporary insulin increase the record would be even more striking. She was delivered of a 12.2 pound healthy baby girl by a cesarean section at term. Note that the insulin requirement of the mother increased after delivery. Two years later she died of disseminated pulmonary tuberculosis.

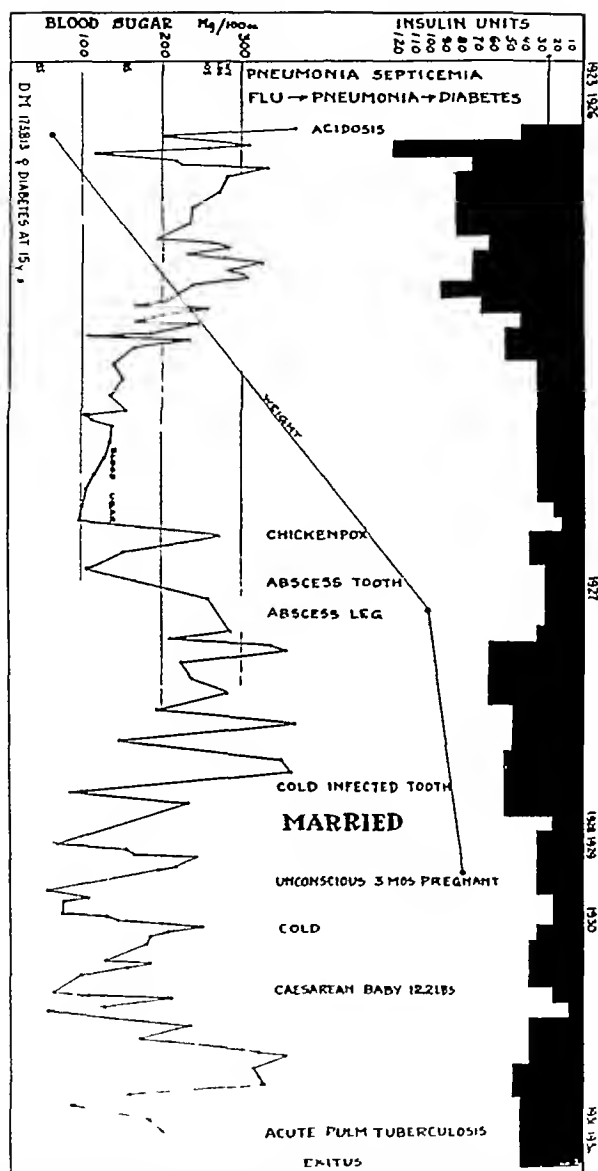


Chart 3—Progress in Case 3. Girl developed diabetes at the age of fifteen years, married at seventeen, gave birth to a healthy baby and died two years later of acute pulmonary tuberculosis.

On a 1,600 calorie diet containing 70 gm. of carbohydrate and as much as 120 units insulin per day, it took nine days to reduce the lipemia.

She made good progress and was discharged from the hospital in three weeks on insulin 10 10 10. In five months her weight increased from 86 to 137.25 pounds, she was a tall girl. She left the hospital with normal blood sugar and sugar free urine. Chickenpox, the first upset, caused a considerable rise of blood sugar, next was an abscessed tooth, then a leg abscess. Insulin had to be increased, and finally when a better control of her condition had been achieved, in September, 1927, she

diminished number of islands, atrophy, and fibrosis—all of which presuppose a diminished insulogenic function in the presence of a demand for an increased function (see Case 1)

In one of the patients (Case 2) diabetes resulted from an infection—whooping cough—which was followed by Vincent's angina of the throat. This history is strongly suggestive of the infections affecting the pancreas. I have studied a group of children whose diabetes evolved in a period from two to thirty days following such infections as colds, influenza, measles, mumps, dysentery, pneumonia, tonsillitis, boils, glandular fever, pyelitis, and jaundice.

We know clinically that such infections do affect the pancreas since diabetes follows where there was no diabetes before. Pathologically a good illustration is offered among others in the case reported by Lemoine and Lapasset¹¹ who report a case of an Algerian soldier admitted to the hospital in 1902 with an attack of mumps. On the tenth day he had fever and chills and a swollen testicle. On the fourteenth day the temperature was normal, and the patient was discharged. On the fifteenth day he felt bad and vomited. The temperature was normal, but he had an epigastric tenderness, and the spleen was palpable. He became jaundiced, the vomiting increased, and on the sixteenth day he died. The postmortem examination showed a swollen and edematous gallbladder. The pancreas was three times its normal size (weight 190 gm.) edematous and congested; the lymph glands were swollen. Histologically the acini were enlarged, the islands, diminished.

CONCLUSION

Four cases of diabetes in childhood and adolescence came to autopsy. Of the four, one followed hyperthyroidism, and three followed infection. One patient died of adrenal insufficiency, two of coma, and one of tuberculosis. Diabetes was present less than a year in the first patient, six years in the next two, and eight years in the fourth. Three of these showed pathologic changes in the pancreas and in the liver.

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The postmortem diagnosis was bilateral chronic ulcerative pulmonary tuberculosis, chronic fibrous pleurisy, bilateral, diabetes mellitus (the islands were well defined), the liver showed advanced cloudy swelling and some fatty degeneration

CASE 4—The patient, a girl, had diabetes at the age of eight years. Of the childhood diseases she had measles, chickenpox, mumps, grippe, and tonsillitis. The onset of diabetes following tonsillitis showed the classical symptomatology. Her family physician prescribed various diets, but she did not get along well. After a year of this, she was placed under my care.

At the time I saw her she had 5 per cent of sugar in the urine and a blood sugar content of 245 (Chart 4). Her weight was 43.75 pounds. She was placed on an 1,800 calorie diet, 80 gm carbohydrate, and as much as 120 units of insulin per day. There was a marked fluctuation of blood sugar. She was discharged from the hospital in four weeks on a 2,000 calorie diet, 120 gm carbohydrate, and 30-30-30 units of insulin. On this routine she was excreting from 2 to 6 gm sugar in twenty-four hours.

To start with, we were dealing with a severe case of diabetes of one year's standing. The patient had a protruding abdomen and markedly enlarged liver. This is a sign which I have learned to regard as unfavorable, for diabetic patients with a fatty liver do not do well, their metabolism has been deranged far beyond a disturbance of carbohydrate metabolism—it involves metabolism at large.

In two months, because she started to have insulin reactions, her insulin had to be cut down considerably for a period of about six months, then it had to be increased. Her weight during this time increased, and except for the protruding abdomen, she looked well.

In January, 1931, she developed a cold. Acidosis developed, her family physician cut out all insulin because of vomiting. She went into a coma and was brought into the hospital on the fourth day. Her blood sugar at 12:30 M was 99 $\frac{1}{2}$, CO₂, 9.9, urea, 60. Twenty units of insulin were given intravenously, at 1:00 P.M. her blood sugar was 1,200, and she died at 1:20 P.M.

Clinically she had been making a slow improvement, but there were no changes in the size of the liver. Acidosis resulting in coma, which was badly managed, ended her eight years of diabetes.

The postmortem showed the following:

- 1 Atrophy of the islands of Langerhans, pancreas 37 gm
- 2 Fatty degeneration of the liver, which weighed 2,250 gm
- 3 Subacute and chronic interstitial myocarditis
- 4 Acute nephrosis
- 5 Persistent thymus (normal for the age)
- 6 Multiple follicular cysts of the ovaries

DISCUSSION

In a study of 9,000 cases of thyroid disease, I found 207 cases, or 2.3 per cent, of permanent diabetes.¹⁰ Such an incidence of diabetes is higher than the incidence generally. The question one cannot answer is: Was the hyperthyroidism, the increased metabolism, and therefore the increased consumption of food which accompanies it the sole cause of diabetes, or was it merely the precipitating factor, superimposed on a diabetic "anlage"? I am inclined to think the latter supposition correct but, of course, cannot be sure. Be that as it may, a pathologic explanation for diabetes is found in the pancreas itself—a

Babinski sign was positive bilaterally and the Brudzinski sign was positive. Examination of the back showed marked tenderness in the lumbar region. There was no particular localization of the tenderness, and swelling was not present. A lumbar puncture showed a cloudy fluid xanthochromic, with 482 cells practically all polymorphonuclear. The smears showed gram positive cocci morphologically identical with staphylococci. A cisternal puncture at the same time showed a clear fluid with 138 cells, 50 per cent polymorphs and the smear and culture were negative. Blood count: 70 per cent hemoglobin 4390 000, R. B. C. 7250, W. B. C., with 66 per cent polymorphonuclear neutrophil leucocytes. Blood culture was positive for staphylococci. The urine was negative. The Wassermann and tuberculin tests were negative.

On September 12 her condition was unchanged. September 13 she complained of pain in her left wrist. Roentgenograms of the spine showed what was thought to be an epiphysitis involving all of the dorsal and lumbar segments. The next day the blood count showed 81900 W. B. C. and 88 per cent P. M. N. There was a marked swelling in the region of the second lumbar vertebra. September 15 she was given a transfusion of 510 c.c. of whole blood by the direct method. Two cubic centimeters of staphylococcus bacteriophage was given subcutaneously daily. The following day a localized abscess appeared on the left ankle. The blood cultures of September 12, 15, 16, 18 and 19 were positive for staphylococci. On September 19, the child was operated upon. Examination of the patient on the operating table showed a large diffuse fluctuant mass over the second, third, and fourth lumbar vertebrae. A longitudinal incision about 4 inches in length was made over the spinous processes; this revealed the mass to be a large abscess which extended below the muscle layer above and below. A culture was taken of the pus which escaped. The report named gram positive cocci, morphologically identical with staphylococcus. About eight ounces of thick purulent pus were evacuated. The spinous processes were then exposed, and the spine of the second lumbar vertebra was visible denuded of periosteum. There was osteomyelitis of the second lumbar vertebra. The spinous process was removed and the laminae opened, free pus escaped. The spinal canal in the region of the second lumbar vertebra was then explored. The dura was found to be inflamed and partially destroyed in this region. No free pus escaped from the subdural space. The wound was packed with vaseline gauze. Patient left the operating table in excellent condition.

On September 20, the blood culture was negative for the first time, and the bacteriophage was stopped. The following day the temperature did not go above 99.6 F. The child showed definite improvement. The operative wound discharged a large amount of seropurulent pus around the vaseline gauze pack for several days. By September 29 the hemoglobin had fallen to 46 per cent, and she was given a second transfusion of 320 c.c. of whole blood. The wound continued to discharge and was slow in granulating. It was repacked with vaseline gauze. The child's general condition continued to improve slowly. October 19, one month after operation and drainage, a cisternal puncture showed three cells, no globulin, 73 mg of sugar, and the smear and culture were both negative. By October 25, the back wound had ceased discharging and was granulating. The abscess on the left wrist was incised, and about 1 dram of pus removed. The culture was morphologically identical with staphylococcus. By November 2, the back wound was practically healed, and on November 8, the child was discharged to the convalescent home at Farmington.

Feb. 6, 1932, a sequestrum was removed from the back wound, but physical examination at this time (Mar 28 1932) shows all wounds to be completely healed. There are no paralyses. There is no limitation of motion in the spine, and the child walks normally.

PERIMENINGITIS

STAPHYLOCOCCUS SEPTICEMIA COMPLICATED BY OSTEOMYELITIS OF THE SECOND LUMBAR VERTEBRA

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EPIDURAL abscess and a complicating meningitis as a result of blood stream infection are now accepted as a distinct entity Schmalz,¹ Pincoffs,² Dandy,³ Gay⁴ and Rosamond⁵ have all reported cases

Despite its definite symptomatology which permits of accurate diagnosis, the number of recoveries reported are few, and most of these patients have had residual paralyses and serious dysfunction because of the location of the infection

The following case is of interest because of the complete recovery after such a serious illness

The case reported is primarily a case of staphylococcus septicemia which resulted in an osteomyelitis of the second lumbar vertebra and was further complicated by an involvement of the spinal cord and meninges with a resulting perimeningitis.

Osteomyelitis of the vertebrae is decidedly uncommon, and perimeningitis is still more so. The mortality in cases such as these is high. Because of the successful outcome the case reported here, an outline of the treatment is included

L. L., aged fourteen years, was admitted to the Children's Hospital of Michigan on Sept 11, 1931, with the complaint of fever and pain in the back.

On Sept 2, 1931, the child complained of pain in the back. The following days she did not eat well and complained of her back from time to time. On September 5, the pain became more severe and radiated to both flanks, however, as long as she was quiet, the pain was not severe. On September 6, she was taken in an automobile to a physician and walked into his office. She walked with a stiff back and complained that motion increased the pain. The following day her temperature rose to 103° F, and she was delirious. September 8 and 9, her condition continued to become worse. She was irrational from time to time and complained of excruciating pain upon the slightest motion.

Physical examination Sept 10, 1931, at the time of admission to the hospital revealed a white female child who appeared acutely ill. There was generalized hyperesthesia. Examination of the ears, eyes, nose, and throat was negative. The neck was held rigidly although there was no opisthotonos. The chest revealed a normal heart and lungs. The abdomen was flat and symmetrical. There were no palpable masses. Tenderness or rigidity were not present. The knees were flexed, and there was pain upon extension of the legs. The knee jerks were present. The

From the Children's Hospital of Michigan.

Babinski sign was positive bilaterally and the Bruzinski sign was positive. Examination of the back showed marked tenderness in the lumbar region. There was no particular localization of the tenderness, and swelling was not present. A lumbar puncture showed a cloudy fluid, xanthochromic, with 482 cells practically all polymorphonuclear. The smears showed gram positive cocci morphologically identical with staphylococci. A cisternal puncture at the same time showed a clear fluid with 138 cells, 50 per cent polymorphs and the smear and culture were negative. Blood count 70 per cent hemoglobin 4300,000 R B C 7,250, W B C., with 66 per cent polymorphonuclear neutrophil leucocytes. Blood culture was positive for staphylococci. The urine was negative. The Wassermann and tuberculin tests were negative.

On September 12, her condition was unchanged. September 13 she complained of pain in her left wrist. Roentgenograms of the spine showed what was thought to be an epiphysitis involving all of the dorsal and lumbar segments. The next day the blood count showed 81,900 W B C and 83 per cent P.M.N. There was a marked swelling in the region of the second lumbar vertebra. September 15 she was given a transfusion of 510 c.c. of whole blood by the direct method. Two cubic centimeters of staphylococcus bacteriophage was given subcutaneously daily. The following day a localized abscess appeared on the left ankle. The blood cultures of September 12, 15, 16, 18 and 19 were positive for staphylococci. On September 19 the child was operated upon. Examination of the patient on the operating table showed a large diffuse fluctuant mass over the second third and fourth lumbar vertebrae. A longitudinal incision about 4 inches in length was made over the spinous processes; this revealed the mass to be a large abscess which extended below the muscle layer above and below. A culture was taken of the pus which escaped. The report named gram positive cocci, morphologically identical with staphylococcus. About eight ounces of thick purulent pus were evacuated. The spinous processes were then exposed, and the spine of the second lumbar vertebra was visible, denuded of periosteum. There was osteomyelitis of the second lumbar vertebra. The spinous process was removed and the laminae opened, free pus escaped. The spinal canal in the region of the second lumbar vertebra was then explored. The dura was found to be inflamed and partially destroyed in this region. No free pus escaped from the subdural space. The wound was packed with vaseline gauze. Patient left the operating table in excellent condition.

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SUMMARY

1 An unusual complication of a staphylococcus septicemia is presented

2 The case demonstrates the value of open operation in the treatment of perimeningitis

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749 DAVID WHITNEY BUILDING

PULMONARY LESIONS RESEMBLING PNEUMONIA AS THE RESULT OF ALLERGIC SHOCK

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IN ANIMALS which survive anaphylactic shock following an injection of antigen, the syndrome of protracted shock occasionally develops. Zinsser¹ describes the following as its manifestations: dyspnea, irregularity of breathing, partial pulmonary emphysema, and fall of blood pressure drop in temperature which is followed by a moderate degree of fever. Dean and Webb² state that in the more severe cases of anaphylactic shock in dogs which did not terminate fatally, another train of symptoms occurred after the acute state had subsided: dyspnea, fever, diarrhea, stupor, vomiting and general malaise. In guinea pigs Ratner and his coworkers³ produced a similar if not an identical condition by means of continued exposure to the antigenic substance after the production of shock. It is possible that Ishioka,⁴ Busson,⁵ Friedberger⁶ and Fried⁷ refer to the same syndrome when they speak of "sterile anaphylactic pneumonia." They produced this condition in guinea pigs sensitized to horse serum upon insufflation of horse serum into the trachea. The lesions which thus arise under properly controlled conditions may either offer the picture of interstitial bronchopneumonia, or they may involve whole lobes. The authors noticed in the lungs hemorrhagic infarctions of various sizes associated with inflammatory lesions. The mode of production of these lesions, their aseptie character in the early stage, the presence of lymphocytes suggested to them a pathologic differentiation from true pneumonia.

One of us has recently⁸ reported cases of severe allergic shock following injection of extracts of cottonseed and horse hair. In two cases eight and twenty hours, respectively, after the injection and after the subsidence of the primary symptoms slight fever, rales in the lungs, and areas of impaired percussion developed. The clinical picture of a low grade bronchopneumonia ensued which lasted for three to four days.

A similar occurrence was encountered following the ingestion of an aspirin tablet in a patient with severe asthma. In this case evidence of pulmonary edema developed about eight hours before the pulmonary infection arose. The pneumonic process lasted for four days; the highest temperature was 102° F.

During the course of studies on so-called "thymic death," one of us presented clinical and pathologic evidence that many, if not all cases thus diagnosed are identical with allergic shock. In a large percentage

of these patients after there had been a sudden collapse, dyspnea, and wheezing, the clinical picture of an atypical pneumonia developed. The following is a typical case

CASE 1—S L., one year old, male, had been in perfect health except for frequent nasal catarrhs (allergic?) No family history was obtainable because the child was a foundling. About one week before death he had an afebrile upper respiratory catarrh from which he recovered in several days. On the morning of the day of death he seemed playful and in good health, the temperature being normal. At 10 A.M., while drinking a glass of milk, he suddenly became cyanotic, dyspneic, and vomited. The cyanosis and dyspnea increased, moist râles were noted in the lungs, and signs of consolidation developed. At noon the temperature was 102° F by rectum, at 3 P.M. the temperature had risen to 103° F, and at 6 P.M. the child expired. The postmortem examination (Dr L. Parker, at Kalamazoo, Mich.) showed throughout both lungs, dilatation of capillaries, exudation of fluid into the alveoli and extravasation of blood cells, areas of emphysema alternating with atelectasis. Some of these lesions showed leucocytic infiltration as seen in early pneumonia. There was some congestion of the spleen and kidneys, the adrenals were not examined. There was a hyperplasia of the bronchial and mediastinal lymph glands and of the thymus (40 gm.) Other organs, particularly the heart, were found normal.

In this as well as in the other cases studied, the microscopic appearance of the lungs suggested that there was a primary edema of the lungs associated with atelectatic and emphysematous areas upon which the infectious process seemed to be superimposed. This was particularly noticeable in some of the slides in which the leucocytic infiltration involved only the marginal parts of the edematous lesions. Such causes as asphyxial death by food lodged in the trachea, infection of atelectatic areas of the lungs, or primary bronchiolitis could definitely be ruled out by the autopsy findings.

Considering this evidence for the explanation of this type of pulmonary infection, we thought that it would be of value to establish certain clinical features which will lead to a proper recognition, evaluation, and therapy of this condition. Such an attempt was made by studying the records of twelve asthmatic children who had been admitted to the Children's Hospital of Michigan on account of pneumonia. In five, the onset and clinical course did not differ from the usual type of pneumonia. There were chills, high temperature, marked prostration, and the usual physical signs of pneumonia. In seven cases, however, there was an afebrile period ranging from six hours to five days, which was characterized by wheezing and dyspnea and by collapse. During this stage there were crepitant râles in the chest, and in two cases blood-streaked sputum was expectorated. The average leucocyte count was 16,600, the average highest temperature, 102.3° F, the average duration of the febrile period, four days. On the whole the disease was much milder than bronchopneumonia. The x-ray examinations revealed a generalized mottling of the lungs, particularly of the lower areas. Toward the end of the febrile period there was either a slight residue of a bronchopneumonic process and prominence of the hilum shadow, or the picture was entirely negative. The following are two typical instances

which are of particular interest because the patients had been seen by us shortly before and during the development of this condition.

CASE 2—F II., a one-year-old girl, with a family history of allergy had been under our care for the preceding four months on account of asthmatic attacks. She had been found sensitive to various substances showing particularly strong reactions to orris root, cattle hair, and apples. The asthmatic seizures always appeared to be very severe and on several occasions were followed by fever.

On Apr 4, 1934, she was seen in the afternoon in a severe attack of asthma, showing evidence of collapse. The temperature then was 97° F. The chest showed asthmatic rhonchi, some hyperresonance throughout, and no impairment of the percussion note. Epinephrine in doses of 1/10 to 2/10 c.c. was given repeatedly with out effect. Three hours later the child had to be admitted to the hospital, extremely cyanotic and in a state of shock. The temperature was 102° F. the pulse 140, the respirations, about 60. In contrast to the lung findings a few hours before, there were fine râles in both lower lobes anteriorly and posteriorly, as well as some asthmatic bruits. There was a general hyperresonance throughout, no areas of dullness could be made out. After rising to 103° F., the temperature dropped on the following day and remained about 100° F. for four days. During this time the asthmatic bruits were heard, but considerably less than before. A marked improvement in the condition set in with the drop of temperature. The white blood count taken on the day after admission was 8,000, the following day, 9,500. The cough had been dry and nonproductive at first and became looser following the second day. An x ray picture of the chest taken on the third day revealed a slight increase in the hilum markings, but no consolidation.

This case resembled in appearance those following injections of an overdose of antigen or ingestion of a drug to which sensitivity exists. The extreme degree of shock and the sudden recovery on the following day was particularly dramatic in this case. It is likely, but could not be definitely determined, that some food to which the child was sensitive, had caused the shock. This is suggested by the fact that similar attacks of lesser severity had occurred previously following the ingestion of food to which the child reacted on skin test.

CASE 2—A. K., an eleven year old boy, had been under our care on account of asthma which was present since infancy. He was found sensitive to various foods and pollen, particularly to tomatoes and short and long ragweed. On Dec. 18, 1933, he was seen in the out patient department during a severe attack of asthma. The following morning a slight fever, which was said to have ranged between 99° and 102° F., developed. He was admitted to the hospital on the third day of the illness in a state of collapse. There was some cyanosis. A dry nonproductive cough was present. Crepitant and subcrepitant râles were heard over the base of both lungs, more marked on the right side. There were considerably fewer asthmatic rhonchi than on examination three days before. A roentgenogram of the chest showed a process approaching consolidation opposite the right lung root. There was also a definite peritruncal infiltration in the right lower lobe suggesting an "acute process." On admission, the third day following the onset of fever the white blood count was 8,000, five days later, 15,800. After the child had been in the hospital three days, the temperature became septic in type, varying between 98° and 104° F. daily, for another week. During this latter period no asthma was present. Râles were heard in various portions of the lungs.

At the beginning of the ragweed season, the child developed hay fever followed by shock pulmonary edema and fever and died within three days. At autopsy the thymus weighed 35 gm. the lungs showed edematous hemorrhagic lesions with beginning pneumonic patches.

Outside of the fact that wheezing inaugurated this illness, it is interesting to note the relatively low blood count during the first part of the illness, after fever had already been existent for three days

The characteristic feature in these cases is the development of a low-grade pulmonary infection following an afebrile period with severe asthma and the evidence of pulmonary edema which was associated with shock. While there cannot be any doubt as to the secondary character of this pulmonary process, it is difficult to ascertain from the clinical evidence alone whether we are dealing with a primary allergic edema of the lungs or whether the infection is due to localized atelectasis resulting from plugging off of smaller bronchi by mucus. However, the evidence which one of us has presented (Waldbott⁹) elsewhere on the pathology of allergic shock points to the former explanation. This conception is further strengthened by the following observations:

1 Urticaria in the lungs. Cole and Korn¹⁰ recently described a case of generalized urticaria in which the edema appeared to have spread down through the mucosa of the bronchi into the lungs. The patient finally succumbed to pneumonia.

2 Analogy with allergic processes in other organs. There is a growing belief that the allergic wheal may involve any organ of the system. It has been brought out by Kline and Young¹¹ that inflammation of such lesions is not uncommon. The best known instance of such a development is the occurrence of nasal and paranasal infections following hay fever and other types of vasomotor rhinitis. One of us (Waldbott¹²) has made similar observations on the trachea and the upper bronchial tree by describing the clinical syndrome of allergic bronchitis. Young and Kline showed that an analogous process may occur in the appendix as well as in other parts of the gastrointestinal tract.

3 Sudden death in asthma with pneumonia. MacDermid¹³ described the case of an asthmatic individual in whom an injection of horse serum was followed by pneumonia. At autopsy hemorrhagic areas were present throughout the lungs associated with bronchopneumonia. He concluded that these lesions were the result of allergic shock. His microscopic sections, which we had the privilege to examine, illustrate more than any other autopsy material on record how infectious processes may arise from hemorrhagic edematous areas due to shock.

In his papers on the pulmonary lesions of shock Moon¹⁴ pointed out that a similar edema in the lungs may occur following such conditions as toxemia of pregnancy, infectious disease, burns, and intestinal obstruction. For the explanation of the edema which was not secondary to any cardiac or kidney changes, he referred to the work of Dale, Laidlaw, and Richards on histamine shock and considered its origin as being due to a histamine-like substance. Whether he is dealing with an allergic phenomenon and whether the condition which he described is identical with the lung findings in allergic shock is difficult to say. There may possibly be a relationship between the lesions under consideration here

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TABLE I
THE NUMBER OF EXAMINATIONS PER INFANT

Infants with one examination	43
Infants with two examinations	38
Infants with three examinations	46
Infants with four examinations	6
Total number of infants	133
Total number of examinations	281

babies from syphilitic mothers, nine infants with eczema, five premature infants with birth weights from 2.0 kg to 2.2 kg and sixteen infants showing minor disturbances, such as upper respiratory infections, mild diarrhea, mild constipation, and questionable hypertonicity. As a careful examination and comparison of the roentgenograms failed to show any distinguishing features, the normal and abnormal cases are all considered together as representing a group of average nursery babies.

The barium meal consisted of 5 cc of a 2 per cent gum arabic solution mixed with 8 gm of barium and added to each ounce of the infant's usual formula. (The majority of the group were on whole milk, water and dextrin maltose mixtures, averaging approximately 45 calories per pound.) The meal was bottle fed. Immediately after completion of the feeding, the infant was rotated on the right side and the first x ray exposure was made with the rays passing through the left post axillary line (Fig. 4). This position was used in an effort to portray the pylorus and duodenum better. The progress of the meal through the gastrointestinal tract was then followed by posterior anterior films made at one and one half hours, three hours, five hours, eight hours, and twenty four hours after completion of the meal. The infants were placed in no special position during the process of digestion of the meal. In the series of the 133 infants the regular feedings were continued at four hour intervals. In a special series of ten infants nothing was given by mouth until the stomach was empty.

The barium enema consisted of 5 cc of 2 per cent gum arabic solution and 8 gm. of barium for each ounce of water. About 30 cc was given through a small catheter. Following the enema a film was made in the posterior anterior position.

The gum arabic solution was added to the barium mixture for both the meal and enema, as it was found, in our experience to give better suspension of the barium and a better filling of the stomach and intestine. When barium alone was given without the gum arabic solution, the meal tended to precipitate out and form a small ball in the stomach and intestine and gave poor visualization. Furthermore, the gum arabic barium meal does not tend to constipate the infant as much as is sometimes noted the barium alone does.

OBSERVATIONS OF THE BARIUM MEAL

1 *Esophagus*—No attempt was made to visualize the esophagus. It was, however, seen seven times in the 281 examinations on the film made immediately after completion of the barium meal. It did not continue to show on subsequent examinations, nor was it present on examinations made on the same infant at different age periods.

2 *Stomach*—a Shape. The infant stomach does not tend to assume fairly definite types or forms as does the so-called "adult type" of stomach. In our series we are unable to classify infant stomachs into

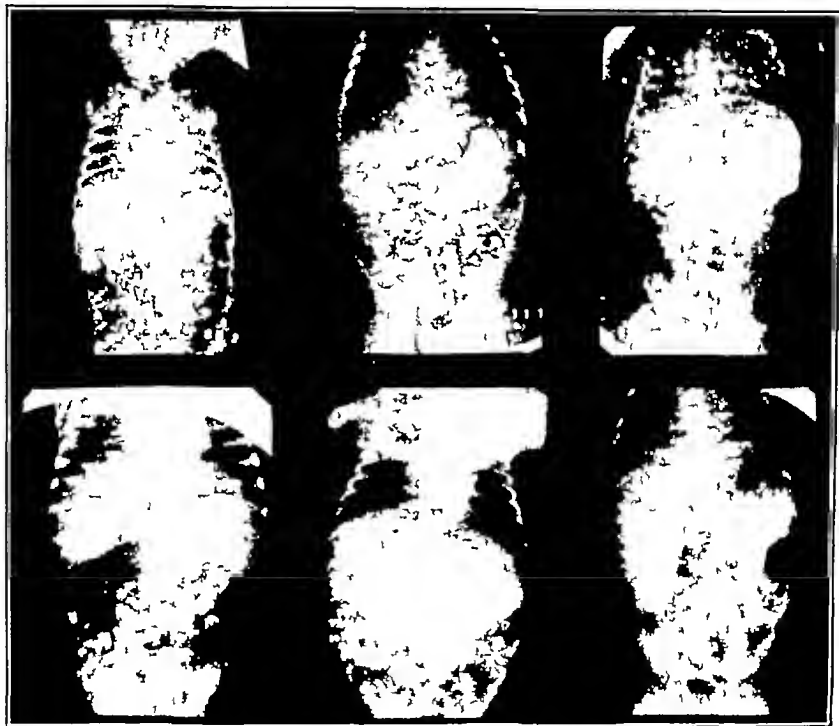


Fig 1 Roentgenograms of stomachs of six infants from 3 weeks to 4 months old showing different sizes and shapes.

definite types. They appear to assume many shapes from "pear shape," "oval shape," "retort shape," "tobacco pouch shape," to intermediate shapes which we were unable to classify. The stomach may change from one type to another or may assume several different shapes during the process of emptying and at different ages in the same infant. In the series we found five stomachs which appeared as "steer horn" type and one stomach which appeared as "fishhook" type. Even in these cases the stomach assumed different shapes during the process of emptying and also at subsequent examinations (Fig 1).

b *Size* The size of the stomach is difficult to estimate. It appears to vary greatly during the process of emptying and at subsequent examinations made on the same infant at different age periods. Usually it extends from the dome of the left half of the diaphragm to just beyond the midline of the spine. However, it may appear greatly enlarged if there is a large accumulation of gas, and in several cases it appeared to extend across the entire abdomen (Fig 1).

c. *Position of the Stomach* The infant stomach varies from the horizontal to the oblique and almost vertical position. From our series we found the horizontal position to be far more frequent. The position from the horizontal to the oblique may change in different examinations on the same infant, and also during the period of emptying of the stomach.

TABLE II
POSITION OF THE STOMACH AFTER BARIUM MEAL

Horizontal	265
Vertical	3
Oblique	13
Total examinations	281

Any classification into horizontal, oblique, or vertical positions is more or less arbitrary, as there is a great variation in the different angles, and at times it is difficult to determine whether it should be called horizontal or oblique.

d. *Height of the Lower Pole* The height of the lower pole varied from the top of the first lumbar vertebra to the middle of the third lumbar vertebra as shown on the film taken immediately after the barium meal. It was noted that the height may vary at different examinations of the same infant from one to one and one-half vertebrae, and also during the process of emptying.

e. *Peristalsis* Peristaltic waves were rarely seen in our series. In the series of 133 infants, only five examinations showed peristalsis, two on the immediate films and three on the one-and-one-half hour films. In the special series of ten infants, in whom nothing was given by mouth following the barium meal until the stomach was empty, films were made at two minutes, 5 minutes and 10 minutes after the meal was begun, and then every half hour until the stomach was empty. A total of 137 films were made on these ten infants and even with the comparatively short time intervals between each film peristalsis was rarely seen.

f. *Air Bubble* It has been observed by Dr W W Wasson and others that soon after the first inspiration of the newborn infant air can be demonstrated in the stomach by x ray pictures. This air bubble changes size and shape during different examinations and during the process of emptying. Though no definite conclusions can be drawn, it appears to exert no influence upon the emptying time of the stomach.

It is situated in the cardia of the stomach and in some cases appears to increase in size as the stomach empties

g Emptying Time The films taken immediately after completion of the barium meal showed the presence of the meal in the small intestine in 244 out of 281 examinations. This would seem to indicate that the stomach begins to empty very soon after the meal is given. This was borne out by fluoroscopic examination of three cases and in the special series of ten cases, which showed small masses in the small intestine in from five to ten minutes after the beginning of the meal. The emptying time of the regular series of 133 infants as checked by films taken one and one-half hours, three hours, five hours, and eight hours after the completion of the barium meal is shown in Table III

TABLE III
VARIATION IN THE EMPTYING TIME OF THE STOMACH

	NO	PERCENTAGE
Emptying time at one and one half hours	5	2
Emptying time from 1½ to 3 hours	27	9
Emptying time 3 to 5 hours	56	19
Emptying time 5 to 8 hours	80	27
Emptying time more than 8 hours	123	43
Totals	281	100

NOTE The true emptying time may be obscure as the estimation of the amount of barium residue appearing on the film is quite difficult. The residue in some cases appeared to be a large amount, while in others it was only a small amount. When the stomach showed only a few flakes, apparently adherent to the gastric mucosa, it was considered as empty (See Fig 4, series 2)

In some cases there appeared to be rapid emptying during the first few hours, then somewhat slower emptying. In several cases in which the small intestines were apparently empty in from five to eight hours, the colon was fairly well filled; and there appeared a gastric residue. The emptying time of the stomach does not tend to be the same at different examinations of the same infant. An example of this is shown in one of the infants whose stomach emptied in one and one-half hours at one examination, in five to eight hours, and in more than eight hours on the second and third examinations. It must be noted that the above data applies to those cases which were given the regular formula four hours after the barium meal. The ten special cases in which no food was given following the barium meal until the stomach was empty showed a slightly different time of emptying. Five of the ten infants showed an emptying time of from three to five hours, and five infants, from five to eight hours. None of these showed a residue at the end of eight hours. If we may be allowed to draw conclusions from this small group, it would appear that feeding the infant within the four-hour period, or before the stomach was empty, did tend to lengthen the emptying time.

h. Pylorus The pylorus was seen on the immediate film in only eleven instances out of 281 examinations. It was more frequently seen on the one and one half hour films (fifty eight times) and on the three hour films (thirty two times). It does not appear to be as well marked in the infant as in the adult (Fig 2). In the special series of ten cases, with the films made at frequent intervals it was not seen until about one and one half hours and then infrequently. Three infants were given the meal and its progress was watched under the fluoroscope. The stomach was palpated to fill the duodenum. In these cases it was noted that the pylorus was not well defined.

3 Small Intestine—As the stomach began to empty the small intestine became visualized by small separated irregular masses of barium. In the special series of cases these barium masses appeared between five and twelve minutes after the beginning of feeding (Fig 2). In the general series they were seen in 244 out of 281 examinations on the immediate film made after the completion of the feeding.

a Duodenum The duodenum was rarely seen on the film made immediately after completion of the barium meal (9 times in 281 examinations). On the one-and one-half hour and three hour films, it was seen twenty times and three times, respectively. A study of the observations under the fluoroscope of the three infants and the special series of 10 cases showed the pylorus and the duodenum to be seen most often from one to three hours after the barium meal. When the duodenum was seen, it differed from the adult appearance. The typical cap was seen only once. Usually it appeared as an annular structure, all portions being approximately of the same size, and curving downward and to the left (Fig 2).

b Jejunum The jejunum was rarely visualized with barium, and, when it was seen, it did not present the "feathery" appearance of the 'adult' type. Instead it appeared sometimes as small isolated masses of barium and other times as a thin continuous line of barium. Occasionally these separated globules were fuzzy in appearance in contrast to the clearly cut masses in the lower part of the small intestine (Figs 2 and 4). The progress of the meal from the pylorus through the duodenum and jejunum was rarely seen in our films.

c Ileum Small globules of barium were frequently seen in the ileum on the immediate and subsequent films as late as five hours. These globules may arrange themselves to show many patterns as more or less isolated from each other, grouped in several bunches, or even grouped in masses in the lower right or left quadrant (Figs 2 and 4).

4 Large Intestine—a Cecum On the three hour film globules of barium were frequently grouped near the ileocecal junction and the cecum often showed partial filling. At five hours it was usually well filled, and at eight hours there were still a large number of examina

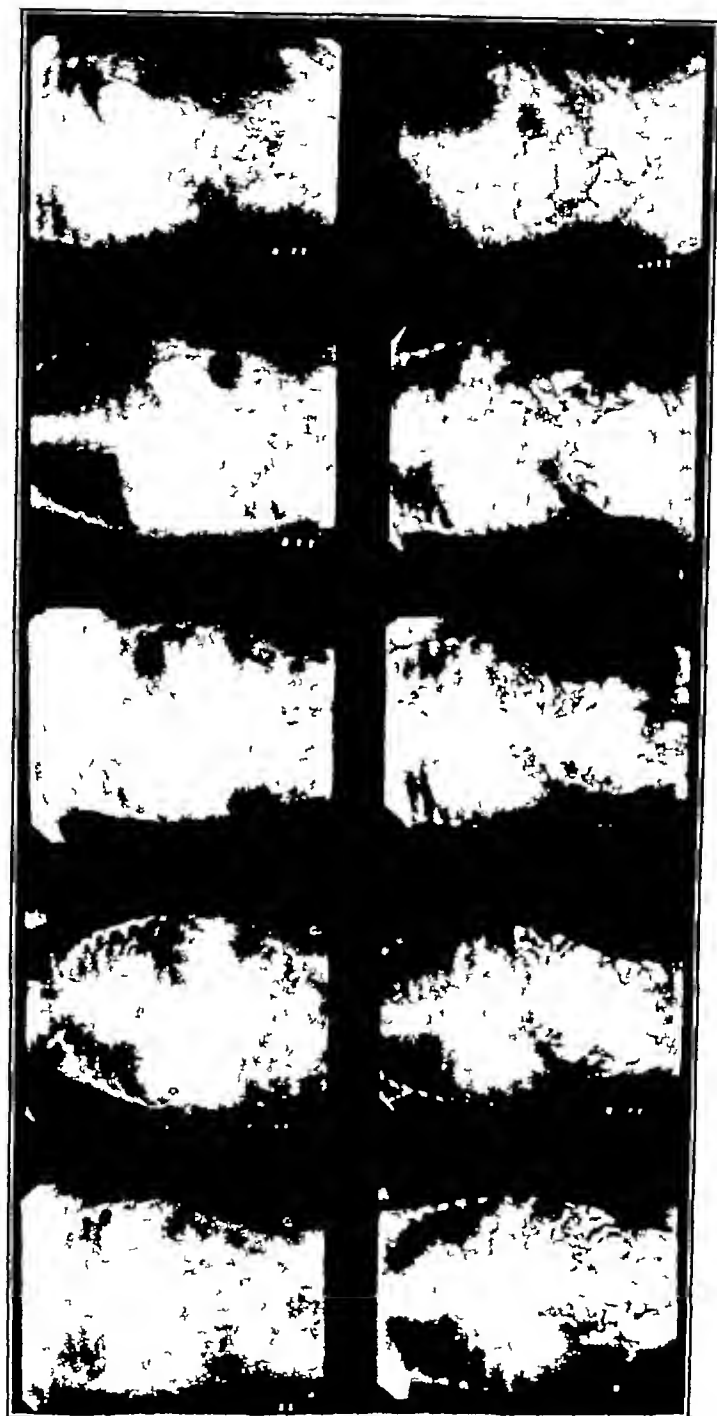


Fig 2—Reproduction of gastrointestinal series in one of the ten special cases
1½ hrs 3 hrs 3½ hrs 4 hrs 4½ hrs 6 hrs
Films taken at 4 minutes 7 minutes, 12 minutes 1 hr
after the beginning of feeding

tions which showed the cecum to be well filled. At twenty four hours there were only two out of 281 examinations which showed the cecum filled and the rest of the colon empty

b *Appendix* The appendix was visualized in only two instances out of 281 examinations. Both visualizations belonged to cases which failed to show the appendix on subsequent examinations.

c. *Colon* Following the barium meal the colon was empty in 9 out of 281 examinations at eight hours. At twenty four hours the amount of filling is shown in Table IV

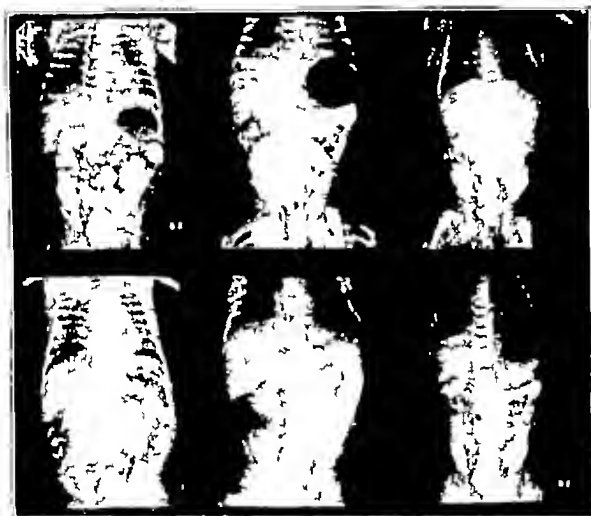


Fig. 1—Roentgenograms of colons after barium enema.

TABLE IV

AMOUNT OF FILLING OF THE COLON TWENTY FOUR HOURS AFTER BARIUM MEAL

Colon—entire colon filled	24
Sigmoid to hepatic flexure	4
Sigmoid to splenic flexure	17
Sigmoid colon alone	64
Cecum alone filled	2
Colon entirely empty	170
Total examinations	281

In those twenty four examinations in which the entire colon was filled and in the four cases in which it was filled from the sigmoid to

the hepatic flexure following the barium meal, it was noted that the haustrations were more marked than shown on the same cases following a barium enema. As there were so few colons filled following the barium meal, a detailed study of the colon was made after the barium enema. The results of the barium enema for a routine study were disappointing. It was found that the infant retained the barium better if no cleansing enema had been given prior to the giving of a barium enema. Even when this technic was followed, the colon in a number of instances did not retain sufficient barium for a long enough interval to allow the making of a satisfactory x-ray exposure (Table V).

TABLE V
AMOUNT OF FILLING OF THE COLON AS SHOWN ON THE ROENTGENOGRAM
AFTER BARIUM ENEMA

Not filled	41
Filled to the sigmoid	16
Filled to the splenic flexure	7
Filled to hepatic flexure	18
Filled to cecum	18
Total cases	100

d *Redundancy of the Sigmoid* All of the barium enemas were studied for the degree of redundancy of the sigmoid (Fig 3). Even in those cases in which there was no filling of the colon, the amount of gas present and the few flakes of barium remaining usually showed the location and course of the sigmoid.

TABLE VI
REDUNDANCY OF THE SIGMOID

Barium enema films not readable	19
Mild redundancy	2
Moderate redundancy	13
Marked redundancy	62
Very marked redundancy	4
Total cases	100

Apparently there was no correlation between the redundancy of the sigmoid and the emptying time of the colon. In the four cases which showed the most marked redundancy and the two cases which showed no redundancy, the emptying time of the colon varied greatly as shown by Table VII.

In cases showing moderate and marked redundancy, the correlation seemed equally impossible as the emptying time of the colon varied in different individuals of the same age and on different examinations of the same individual over a period of months.

e *Spasm of the Colon* Thirty-six cases which showed sufficient barium filling of the colon after the barium enema were examined as to the amount of spasm shown on the films (Fig 3). The results showed no spasm in 20 cases and spasm in 16 cases. The location of the spasm varied in the different cases. As only one barium enema

TABLE VII

CASE NO	TWENTY FOUR HOUR FILM	FINDING
<i>Cases Showing Very Marked Redundancy</i>		
77	1st Examination	Entire colon filled
	2nd Examination	Colon empty
	3rd Examination	Colon empty
82	1st Examination	Colon empty
	2nd Examination	Sigmoid colon filled
	3rd Examination	Sigmoid colon filled
85	1st Examination	Sigmoid colon filled
	2nd Examination	Sigmoid colon filled
	3rd Examination	Colon empty
125	1st Examination	Colon empty
	2nd Examination	Colon empty
<i>Cases Showing No Redundancy</i>		
57	1st Examination	Sigmoid filled
	2nd Examination	Entire colon filled
127	1st Examination	Colon empty
	2nd Examination	Colon empty
	3rd Examination	Sigmoid filled

was given to each infant the location of the spasm was not determined on different examinations of the same infant. Well filled colons after the barium meal rarely showed spasm although after the barium enema these infants sometimes showed spasm. With the barium enema, six infants showed spasm in more than one portion of the colon. There was no significant correlation between the degree of spasm shown in the colon following barium enema and the speed of emptying of the same colons following the barium meal.

f Haustrations Twenty eight infants given barium enema could be examined for the presence of haustrations. No haustrations were found in 16 cases, and haustrations were found in 12 cases. The position and degree of haustrations appeared to vary greatly. They are not as marked as in the adult type of colon. In the same cases the colon as seen on the eight hour and twenty four hour film following barium meal usually showed more haustrations than on the barium enema film.

g Flexures There were thirty-one infants in whom the flexures could be studied. Nine of these showed annular or very poorly marked flexures and twenty two showed angulated flexures (Fig 3).

ABNORMAL CASES

Premature Infants—There were five premature infants with birth weights from 20 kg to 22 kg on whom fourteen examinations were made. There was no marked decrease in the emptying time of the stomach. Of the fourteen examinations made eight showed emptying at five hours, thus showing a larger percentage empty in five hours than that shown by the group as a whole. No other differences were noted. However this series is too small to draw any conclusions.

Eczema—There were nine cases of eczema. The examinations showed no significant changes as compared with the normal group.

Syphilis—The eleven infants from syphilitic mothers also showed no marked changes in the gastrointestinal roentgenograms

Minor Disturbances—Sixteen infants comprising those showing minor clinical disturbances, such as slight constipation, upper respiratory infections, mild diarrhea, and questionable hypertonicity, were not found to differ from the rest of the series in the roentgenologic studies

DISCUSSION

According to the literature, there is great variance in the observations and conclusions in regard to the gastrointestinal tract of infants. We should like to compare some of our findings with those of earlier workers.

There has been a great deal of difference of opinion as to stomach form. Alvens and Husler⁵ described three types of stomach dependent on the taking of fluids in the vertical position, the taking of fluids in the horizontal position, or the taking of gruels of thick consistency in the vertical position. The basis of this classification is the air bubble.

Theile⁶ describe two main types of stomach, the "bagpipe" form of Leven and Bariett and the "tobacco pouch" form of Pisek and Le Wald. However, he states there may be infinite varieties of transitional forms. Pisek and Le Wald stated that there is no definite form of stomach in the infant.

Finally Rogatz⁷ using no contrast medium divided the infant stomach into two main types: (1) the shape of a pear or flask lying on its side with a large, circular fundus and a smaller narrow pyloric area, (2) smooth elliptical or oval in shape, occurring less frequently. He also describes a third form, common to both when thick gruels are ingested, namely, a small circular or oval form about one-third the size of the fluid forms with little or no air bubble at all.

From our observations we are forced to the conclusions, in agreement with Pisek and Le Wald, that there is no constant form of the infant stomach in the roentgenogram and that there are wide variations in different individuals and even in the same individual at various times. In agreement with Pisek and Le Wald, Leven and Barrett, Flesch and Peteri,⁸ Trumpp,⁹ and Rogatz,⁷ we found that the long axis of the stomach is almost always horizontal.

In agreement with Ladd and other workers we rarely found peristalsis in the stomach. Rogatz¹⁰ described a definite "peristolic function," that is the capacity of the stomach wall to surround or grasp its contents following the ingestion of food. This is not to be confused with the more familiar peristaltic function.

The emptying time of the infant's stomach has been studied by various workers and the times given vary greatly. (See Table VIII.)

We have found in normal infants some barium may be visualized in the stomach even after 8 hours. Ladd states that if a feeding is given after the barium meal, there is a tendency to faster emptying. We

TABLE VIII
EMPTYING TIME OF STOMACH

	TIME WITH BREAST FEEDING	TIME WITH ARTIFICIAL FEEDING	AUTHOR
Newborns	2-3 hr	3-4 hr	Vogt ¹¹
Nurslings	3 hr	5 hr	Alwens ⁵
	2½ hr	2½-8 hr	Ladd ³
	3 hr	4 hr	Kerley ¹²
	2-3 hr	3-4 hr	Thiele ⁶
	1½-2 hr	3-5 hr	Kahn ¹³
	1½-4 hr	2½-4 hr	Bessan ¹⁴
		1 hr-40 min	Shukry ¹⁵
		over 3 hr-40 min.	
	3-4 hr		Izumita ¹⁶
	av 3½-4½ hr	3½-6½ hr	Demuth ¹⁷

were not able to confirm this. In our regular series the infants were fed again their regular formula four hours after the barium meal, and it will be noted (Table III) that as high as 43 per cent of these children showed some residue after eight hours. In the ten special cases in which no feeding or water was given after the barium meal until the stomach was empty our longest emptying time was between six and one half and seven hours.

De Buys and Henriques¹⁸ state that motility of the stomach is more rapid when the child is placed in the right lateral position, and comparatively slow in the supine position. In our series the child was usually in the supine position though no attempt was made to have the child in any fixed position.

In agreement with other observers we found that the meal finds its way into the small intestines very quickly after the beginning of feeding. Le Wald¹⁹ states that the duodenum rarely shows the caplike appearance in infants. We found that this was the case and also that the pylorus and duodenum were difficult to visualize. From our observations the infant jejunum does not present the adult feathery appearance. We have not found this previously mentioned in the literature, and we have no explanation for it. The emptying time of the small intestine in children has been studied by Kahn²⁰ who gives the time in stomach as four to five hours, small intestines, as seven to eight hours, large intestines as two to fourteen hours. With dye stuff the entire passage took from four to twenty hours on the average about fifteen hours. De Backer and van de Putte²¹ found that the small intestinal tract is not emptied until after eight hours after two and one-half hours, the contrast meal may be in the cecum, in six to seven hours to the splenic flexure, and in eight hours in the sigmoid flexure, and the entire intestinal tract is free in from eighteen to twenty four hours.

In our series of 281 examinations the eight-hour film showed nine instances and the twenty four hour film, 170 instances in which the entire tract was empty (Table IV). Although there has been a very

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adequate anatomio etudy of the infant colon hy Scammon,²² roentgen etudies of the normal colon seem to have been neglected In a gen eral way our observations bear out tho anatomical findings of Scam mon i.e., haustrations were poorly marked, the sigmoid colon appeared relatively long and redundant and the flexures were not as well marked as in the adult

RÉSUMÉ OF FINDINGS IN AVERAGE CASE

The progress of the meal may be briefly summarized as follows (compare Fig 4)

Immediate film

The etomach began to empty Small globules of barnum were seen in the lower part of the emall intestine The pylorus, duodenum, and jejunum were rarely seen No meal was visualized near the ileocecal junction.

One-and-one half hour film

The etomach still showed a considerable quantity of meal. It was empty in five out of 281 examinations Frequently it had changed its shape from that shown on the immediate film The pylorus, duodenum, and jejunum were more often seen on this examination than on the immediate film. Globules in the iloum had increased in number and were well disseminated or shown as groupings in various patterns The meal had not yet reached the ileocecal junction

Three-hour film

The stomach was empty in thirty two, 11 per cent, out of 281 examinations The pylorus, duodenum, and jejunum were not seen as often as on the one-and one-half hour film. When there was a gastric residue, it varied considerably as to the amount of meal in different cases and different examinations in the same case The ehape had frequently changed from that shown on the previous films Globules of barium were frequently grouped near the ileocecal junction, and the cecum often showed partial filling

Five-hour film

The stomach was empty in eighty-eight, 30 per cent, out of 281 examinations. The pylorus, duodenum, and jejunum were uncommonly seen. Scattered masses were often seen throughout the small intestine, and the colon was usually well filled from the cecum to the middle of the transverse colon, and sometimes to the splenic flexure (twenty four examinations)

Eight-hour film

The stomach was empty in 168, 47 per cent, examinations out of 281. In the 123, 43 per cent, examinations which showed gastric residue, it usually appeared as a very small amount. The gas bubble was often quite large whether or not the stomach was empty The small intestine frequently showed small scattered masses of barium The colon was well filled in ten cases, in the other cases there were isolated masses

of barium The colon and entire gastrointestinal tract were empty in nine examinations out of 281

Twenty-four-hour film

The stomach was empty in all examinations Small intestine rarely showed a few isolated globules of barium The colon was entirely empty in 170 out of 281 examinations (Table IV)

SUMMARY

1 Two hundred and eighty-one roentgenologic gastrointestinal examinations were made on 133 infants (sixty-three boys and seventy girls), aged from one week to six months

2 Barium enemas were given to 100 of these infants

3 The study of the films shows that marked variations may be found between individuals or in any one individual at different times

4 These are illustrated by such findings as (1) the variation in the emptying time of the stomach which is from one and one-half to more than eight hours, (2) the lack of any constant shape of the stomach, (3) the changing pattern presented by the globules of barium in the jejunum and ileum, or (4) the variation in the amount of redundancy of the sigmoid

5 Thirty-four roentgenograms selected from the 1,686 films of these 133 infants have been reproduced to illustrate the individual variations noted

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Critical Review

NORMAL NUTRITION DURING CHILDHOOD

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PREVIOUS reviews of this series have dealt with problems of nutrition in general and with the feeding of the normal infant. This presentation will offer a review of some concepts pertaining to the nutrition of the child from the period following infancy through adolescence and will have as its thesis the desirability of dietary supervision throughout the whole period. Consideration of therapeutic dietary measures will be reserved for presentation at another time.

In review, the quantitative and qualitative food needs of the body stand in direct relationship to the quantity and quality of growth and expenditure of energy. Defects of nutrition may be masked, absence of outstanding disease offers no evidence that the diet is adequate. Food which satisfies the appetite will not necessarily meet the body's needs, in fact, with the types of foodstuffs customarily employed as the chief constituents of the dietary, the likelihood of qualitative inadequacy of such a regimen is great. Within limits the quantity of growth will be determined by the minimal allowance of any of the dietary essentials, in some instances, gross growth may seem ample, yet with minimal intakes of certain essentials the quality of tissue composition may be deficient. Not only are the amounts of the various essentials important, but also the ratio which one bears to another. Fortunately, in any type of mixed dietary usually employed in the average community, many of the phases of the diet will be met adequately without any special consideration. This holds for most of the minerals used in the body and as well for the calories. Potential defects most common in the diet of the child in this country pertain to the amount and quality of protein ingested, the amount of calcium and phosphorus offered and the ratio in which they exist in the diet, and the allowance of iron, iodine, and the various vitamins. Of the latter, certain diets habitually used may approach inadequacy in numerous regards, probably special consideration is required to insure sufficient intake of vitamins D, A, C, G and B, the need for emphasis decreasing in the order named.

The need for supervision of the diet of the infant has been forced into the consciousness of the medical and lay public within the past two decades and now is quite generally accepted and practiced with varying degrees of thoroughness and insight. From the emphasis placed on the diet of the infant, one might conclude by inference that the nutritional needs of the infant differ in some significant manner from that of the human organism at any later period of life. While the state of infancy does offer certain nutritional problems peculiar to that age of life, the

of barium The colon and entire gastrointestinal tract were empty in nine examinations out of 281

Twenty-four-hour film

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may not be taken into consideration. Recognition of the inadequacy of such measurements for this purpose fortunately is gaining ground, a child may weigh less than the standard value for his height yet not be abnormally thin, on the other hand, he may exceed his predicted value and still be malnourished. Attempts have been made to differentiate the desirable weight ratios for children of varied types of habitus through recognition that the size of the skeleton will determine the amount of soft tissues appropriate for an individual child.^{2, 4, 5} Through such means a fairer evaluation of the quantitative aspect of nutrition may be gained. Physical measurements become much more valuable if obtained at successive intervals on the same child and comparisons made as to the rate of gain. However, many factors other than anthropometric measurements must be considered in estimating the adequacy of nutrition in all its aspects. Such measurements may detect the presence of marked under or overnutrition, but usually will not reveal the perversions of nutrition for which the term 'malnutrition' might well be reserved. Some of these manifest themselves in symptoms or signs which are more or less pathognomonic but which often represent the existence of a vicious cycle usually involving nutritional disturbance as an important link. These may reflect themselves in alteration of the turgor of the tissues, color of the skin and mucous membranes, degree of alertness, or in evidences of apathy or irritability, poor posture, restlessness, disturbed sleep or other signs of chronic fatigue.⁶ The demonstration of appreciable degrees of dental decay or the history of habitual constipation usually may be accepted as sufficient evidence that perverted nutrition exists. Laboratory procedures such as roentgenograms of bones, determination of the levels of various constituents of the serum or metabolic balance periods, may reveal evidences of disturbed nutrition which otherwise might be merely suspected or missed.

The results of different nutritional surveys made in various sections of this country may be taken to indicate either the existence of wide spread malnutrition⁷ or that little nutritional disturbance exists except under unusual circumstances.⁸ This discrepancy is dependent in part on the confusion of quantitative undernutrition with the less obvious evidences of malnutrition or perverted nutrition. Evidences of the latter status do not imply conditions incompatible with life or immediately dangerous, but they are significant in their relation to the efficiency and later health of the individual. One finding of significance in these nutritional surveys is that the nutritional status of children seems actually better since the inauguration of relief measures than theretofore explainable on the basis of the increased attention to efficient feeding which the recent regimen of relief has inaugurated.⁹ Data of this type are illuminating, and if dietary conditions can be maintained at the improved levels of efficiency, the level of health of the community can be expected to rise correspondingly. If relief becomes unavailable and the children are left to the type of dietary the depressed economic situation will enforce on most the results will be disastrous. The lessened death rate observed in England during the past two centuries is considered by Harris¹⁰ as dependent in part on the gradually improving level of national nutrition. While this may be taken as evidence of greater availability of suitable foods throughout the year, it must be recognized that financial stress together with unfamiliarity with the types of foods most needed by the body, will tend to lower the nutritional status unless the

services of persons skilled in the science of nutrition are available to assist in the administration of relief measures

Many conditions other than poverty can contribute to the establishment of malnutrition.¹ Adequate nutrition involves adequacy of ingestion, digestion, absorption, utilization, and excretion. These may be affected through organic or functional disturbances, the former may depend on the presence of infections or on mechanical causes, the latter on overactivity of body or of mind, or on poor diet habits. Poverty exerts its effects more through parental ignorance or shiftlessness than through inability to obtain nutritionally adequate foods, suitable expenditure of the same amount for food with a wise choice of foodstuffs would lessen greatly the deficiencies of the diets of the poor. The initial reserve of stored nutritional essentials will condition the appearance of nutritional disturbances.¹ Among mechanical factors conditioning malnutrition, poor teeth, very large tonsils, and nasal obstruction should be mentioned.¹¹ Appetite will be impaired through persistent postnasal discharge. Physical conditions leading to fatigue will lessen voluntary food intake, such conditions include chronic nasal obstruction, poor vision, or difficult locomotion from any cause. Focal infection can contribute through its rôle in producing nasal obstruction, tonsillar enlargement, and postnasal drip, as well as by the effects of the infection per se, such infections seem to have the effect of diminishing the rate of gastroenteric peristalsis, with delayed emptying time of the stomach. The presence of any illness may serve to lessen the appetite and diminish the intake of suitable food. Diseases which are associated with lessened ability for absorption of digested food may induce deficiency diseases even though the intake is ample.¹² The use of therapeutic diets is a source of danger, unless care is employed to make the diets nutritionally complete. Among the functional causes of diet inadequacy, the psychogenic disturbances are most important among the more well-to-do.¹³ These difficulties arise from a basic misconception of the simple facts of nutrition. Under this designation several situations may be included, some of which already have been mentioned. First, the adult members may fail to appreciate the qualitative need for certain types of food for themselves or their children and through either carelessness or ignorance permit the child to choose at will from the foods offered at the table, without any conscious attempt to make the foods offered qualitatively suitable. In general, a child may be expected to adopt the least desirable food habits of his adult associates, this plays a large part in conditioning the type of food intake of the individual throughout his lifetime. On the other hand, overzealous application of imperfect knowledge concerning suitable dietaries may lead to food consciousness of such a degree that eating becomes a burden rather than a routine performance, and the child through rebellion develops into a feeding problem, and malnutrition results even though suitable food is offered. A similar end-result may obtain when the child is permitted to develop poor or irregular habits of eating, sleeping, bowel function, or other necessary physiologic acts.

Many references pertaining to the value of various foods, singly or in combination, have been cited in the foregoing and in previous reviews of this series. The trend of relevant literature has been to substantiate the views presented therein. Numerous reviews have appeared pertaining to human nutrition as a whole.^{1 2 3 10 14} Other studies have dealt with the body's requirement of the various vitamins, minerals, calories

and protein, with the special values offered by various specific foodstuffs, the rôle played by the acid base nature of the diet ash on nutrition and body function, and the relationship of diet to resistance to infection.

Sberman, in discussing trends in the recent advances in the chemistry of food and nutrition, comments on the relation in structure between amino acids and the organic catalysts, such as thyroxine, glutathione, adrenin, and insulin. The important rôle played by the amino acids in the body's functions and the limited ability of the body to synthesize them renders it necessary that the body receive the various essential amino acids in the food in sufficient amounts. A newly identified amino acid, methionine, is recognized as an essential component of proteins. He implies also that casein may contain still other units as yet unrecognized.¹ Considerable danger of inadequate ingestion of first-class protein foods exists among children,¹⁴ this is noteworthy only when the ingestion of milk is markedly curtailed. Sherman points out that low milk diets incur the likelihood of deficient intake of calcium and that this may not be apparent clinically but may result in bone of deficient calcium content. Moreover, under such a dietary there is often a parallel deficiency of vitamins A and G. The low content of calcium in the infant's bones at the time of birth is an aid to its delivery but increases the hazard of the development of rickets during infancy unless ample amounts of that mineral and of vitamin D are supplied. The average daily per capita consumption of milk in the state of Illinois during the years 1929-1931 was less than two thirds of a pint,¹⁵ in England it is much less.¹⁶ The English minimal standards of a pint daily up to the age of five years, and a half pint daily from five to ten years are much lower than those recognized in this country.¹⁶ The customary lowered intake of milk together with lessened sunshine, may account in considerable measure for the high incidence of rickets described by Harris.² He states that a recent survey indicated that 88 per cent of five year-old children in a large group showed evidences of past rickets and that in 1918 11 per cent of the crippling of school children was ascribed to the residual deformities of that disease. In the report of the conference between the Ministry of Health and the Committee on Nutrition of the British Medical Association dealing with the minimal essentials for a complete diet, the value of milk in the diet was stressed especially because of its content of first-class protein, minerals and vitamins, together with carbohydrate and fat all 'in a naturally balanced form.'¹⁶

Less stress is placed on the necessity of special measures to insure sufficient iron intake after the stage of infancy.¹ The infant born at term is safeguarded through the storage in its body of a supply of iron sufficient to meet his needs in some measure for the first few months of life.

Two recent studies relating to the significance of the acid base potentialities of the diet seem significant in view of the prominence given to these factors in the advertising of various foodstuffs. Bischoff, Sansum, Long, and DeWar¹⁷ determined the effect on the plasma bicarbonate and the serum pH of various foods and acid and basic salts. Even when large amounts of foods with acid ash were given, no significant or prolonged alteration in the plasma bicarbonate, serum pH or urine acidity could be established. The eating of a pound of steak had barely more effect than did the ingestion of a quart of milk. A pound of bananas or a quart of orange juice showed no effect on the acid base equilibrium.

Morgan and her colleagues²⁰ studied the response of newly weaned puppies to the ingestion of diets of casein, agar, sucrose, suitable sources of vitamins, and various salt mixtures, the latter were acidic, neutral, and basic. Some animals received vitamins A and D in the form of cod liver oil, while others received only their vitamin A as butterfat. The significance of all the findings is not apparent, but they tend to show that cod liver oil is least necessary when the ash of the diet approaches neutrality and is most needed and most effective with an acid ash diet. The serum chemistry reflected in its changes the nature of the salt mixture employed, but the changes were of minor degree. Low calcium diets led to bone lesions which were more marked than were observed under any other regimen.

Sherman¹ and Harris² both state that the clinical significance of shortage of vitamin B in the ordinary diet is much less important than that of vitamin G. Harris emphasizes the frequency of vitamin D shortage in England, Sherman feels that the overexploitation of that vitamin in this country has been unfortunate, leading to an exaggerated sense of its importance in nutrition. Equal emphasis should be placed on the adequacy of intake of calcium and of phosphorus.

Hess²¹ studied the incidence of night blindness as observed by ophthalmologists, and from the low incidence reported he concluded that deficiency of vitamin A is not particularly common. Jeans and Zentmire²² studied the degree of dark adaptability in a large series of apparently healthy children and found a high percentage of subclinical night blindness, which was corrected through the administration of vitamin A. From their study they are led to believe that there is a widespread deficiency of vitamin A in the diets of children. The significance of vitamin A in relation to infection received the attention of many investigators. Hess²¹ states that respiratory infections of infants are not due to deficiency of vitamin A and usually their incidence cannot be lessened by the use of a diet rich in that factor. His subjects, however, were not observed under conditions of low vitamin A intake. Clausen²³ and Robertson²⁴ have reviewed recently the relationship of nutrition to infection, and their conclusions are similar. Clausen states that susceptibility to infection is not as a rule affected by diet, while resistance to infection may be greatly reduced by deficient diet. The effects of deficiency of vitamins A and C are noteworthy in this regard, and under certain conditions inadequacy of vitamin B may exert a similar effect. According to him, a similar relationship for vitamin D has not been established. Robertson correlates the clinically observed value of vitamins in the prophylaxis against infections with possible suboptimal amounts of these in the diet. Although susceptibility does not seem to be altered thereby, the subsequent course of the infection seems to be modified. If the storage and ingestion level of vitamins already is at an optimum level, little may be expected from further additions, the difficulty lies in the fact that optimum levels for the various vitamins remain to be determined. An experimental study by Greene²⁵ shows that some alterations in serologic characteristics can be obtained through variation in the level of vitamin A available. Rabbits depleted of vitamin A were found less able to produce immune bodies to erythrocytes of sheep or oxen than were well-fed controls or those depleted of vitamin D. A smaller and possibly insignificant difference was noted in the ability to produce agglutinins for injected *B. typhosus* organisms.

Studying a group of over 200 women and children who were living under decidedly unfavorable dietary conditions, Brown, Campbell, Stoner, and Macy observed the effect of adding to the diet 3 gm. of non fermenting yeast daily. They report that beneficial results were obtained as seen in gain in weight and lessening of anorexia and of constipation. No undesirable effects were noted.²⁴ The foods employed by these subjects were deficient in many of the essentials for normal nutrition, including vitamin B. Whether similar results might be expected through supplementing less limited diets with yeast remains open for question.

With subclinical degrees of vitamin C deficiency in mind, Dalldorf²⁵ studied the ease of production of petechial hemorrhages through the application of reduced atmospheric pressure, employing the technique described by Hecht. The apparatus used consists of a glass cup with an inner diameter of 1 cm., and with a flange of 8 mm. width, connected with a device for producing negative pressure and with a manometer. The pressure at which petechiae appear is noted, the standard for each individual must be known, since wide variations in capillary resistance seem to characterize different persons. For this reason, isolated readings offer little or no significance. The values observed in 251 children ranged from 10 to 50 mg. mercury, with an average value of 30 to 40 mg. Among a group of fifty four children living under adverse economic conditions, the average pressure at which petechiae first were observed was 25.4 mg. of mercury, although over 9 per cent had values of over 50 mg. Successive measurements were made in fifty two children, before and in the course of improved diet. Their initial average values were 22 mg., after several months of hospitalization, the averages were up to the level observed in the other children in the hospital. Two children observed daily showed rapid increase in capillary resistance. A rapid improvement might be expected when vitamin C deficiency is corrected, as a corollary of histologic studies of animals studied similarly. The author states that apparently healthy guinea pigs frequently show evidences of scurvy at their costochondral junctions and that twice as much vitamin C is needed to prevent lesions in the incisor teeth of guinea pigs as is necessary for avoidance of frank scurvy. Fragility of capillaries appears in these animals within forty-eight hours after inauguration of low vitamin C diet. Presnell²⁶ found that the blood of scorbutic guinea pigs has a prolonged clotting time, fewer platelets and red corpuscles, and less hemoglobin than their normal controls. These findings antedate any other manifestation of scurvy in these animals but offer no data for humans. The rabbit does not show similar changes after twice the period needed for their production in the guinea pig. Greene²⁷ employed the negative pressure test on children's skin, as described above, studying well nourished preschool children as subjects. He considered the test positive in 22 per cent of the group. The test was also positive in 9 per cent of a well nourished group of older children as compared with a positive incidence of only 8 per cent of a group of malnourished children receiving only a small amount of vitamin C. He emphasizes that a positive capillary test cannot be considered pathognomonic of vitamin C deficiency. The identification of vitamin C as ascorbic acid and its availability in concentrated form in various food stuffs have led to the appearance of ascorbic acid on the market in pure form suitable for administration either by mouth or parenterally. In

health no such measures need be employed, however, since adequate intake can be offered in the form of naturally occurring foods³⁰

Much confusion still exists regarding the relative value of various sources of vitamin D, and at the present it is not possible to draw clear-cut conclusions on the subject. The issue is made more acute through the appearance on the market of numerous foods enriched with "the sunshine vitamin." Sherman's remarks concerning the overexploitation of vitamin D are pertinent in this connection.¹ It is easy to focus attention on this one food essential to the exclusion of others equally worthy of consideration. In general, it probably is very desirable to supplement the intake of vitamin A in a degree parallel to that of vitamin D since often their potential deficiencies run parallel and evidence is accumulating to point to the advantage inherent in the use of vitamin A in amounts greater than those needed to prevent obvious disease.

Various authorities have offered estimates as to the quantitative dietary requirements of mankind. Many of these consider only the adult and will not be discussed in this review. British dietary authorities¹⁰ asked to state as nearly as possible what a safe standard dietary would offer, stated that a desirable daily calorie intake should range from 900 to 1,100 calories during the first two years of life, 1,400 to 1,700 during the third to sixth year, with progressive increase up to 3,000 to 4,000 calories for the adolescent boy, or 2,800 to 3,000 for the adolescent girl. The need for protein consumption in greater amounts by the growing child than the adult is emphasized, also that much of this should be supplied as "first-class" protein, or that which approximates the composition of the body tissues most closely. The value of milk in this connection is stressed. McKay and Evans³¹ observed the intake of children of preschool age and determined that their daily protein intake was equal to about 2.7 gm per kilogram body weight or to 1.1 gm per inch of height. Half of this was supplied by milk, 19 per cent by cereals, 19 per cent by meat and eggs, and 9 per cent by fruits and vegetables. About 13 per cent of the calories were supplied as protein. They remark that this intake seems consistent with the maintenance of health and good physical development. Sherman¹⁰ emphasizes that animal or human organisms may grow to maturity with bodies poor in their content of calcium or of iron if the content of these minerals in the diet is suboptimum, yet such individuals may appear well nourished. Balance studies show that the amount ingested may exceed excretion in the child receiving as little as 0.4 to 0.46 gm of calcium a day, but twice this intake is necessary if optimal retentions are to be observed. Such values are most readily attainable through the daily ingestion of a quart of milk. The desired ratios of calcium to phosphorus in the diet may show wide variation, because of the relative rate of growth of bone and muscle, each of which requires phosphorus for its composition. However, if the dietary intake of calcium and of phosphorus is liberal, no further attention need be paid to the ratio of one to the other in the diet. Sherman also notes that a liberal intake of calcium seems to aid in the conservation of iron, a mineral the metabolism of which usually is considered as wholly distinct from that of the former. He implies that as knowledge is gained, further interplay of function will be detected between various dietary components.

Wait and Roberts³² observed the food intake of a group of well-nourished girls aged ten to sixteen years and computed the amounts of

various dietary factors ingested. Total calories varied from 1,650 to 2,925 per day. Considerable variability in the energy intake of the individual was noted with free-choice diets, ranging from 10 per cent to 181 per cent, averaging 49 per cent. They emphasize that because of this fact, more than four days' observation must be included in evaluating the intake of a child. The average daily caloric intake per day was about 66 per kilogram of body weight for the prepubertal age, lessening progressively through the period of declining growth to a level of 38 calories per kilogram per day at the completion of adolescence. The protein intake paralleled this in large measure, from the level of 2 gm per kilogram at eight to ten years to 1.2 gm. per kilogram at sixteen to eighteen years. Koehn³³ in a similar study of girls from six to thirteen years of age, offered a standard dietary but allowed considerable choice as to size and number of servings and in some measure as to the dietary constituents. The diet eaten had an average caloric distribution of 14.3 per cent from protein, 43.2 per cent from fat, and 42.6 per cent from carbohydrate. Each child was given about a quart of milk daily and as much butter as was desired. The calories per kilogram body weight per day ranged from 75 to 80 for the younger girls to 55 to 60 for the older ones, the corresponding protein intakes were 2½ to 3 gm. for the younger girls and 2 gm for the oldest. The diets were basic, the average total daily intakes of calcium, phosphorus and iron for nine of the girls were 44 mg, 49 mg, and 0.44 mg, respectively. The author concluded on the basis of these observations that under suitable circumstances the child's appetite is an adequate guide for its food needs. Suitable circumstances in this study included the presentation of foods of high biologic value and surroundings conducive to their ingestion. Hubbell and Koehn³⁴ studied the retentions of calcium, phosphorus, and nitrogen by these same girls, under diets of the type described. These consisted of cereals equivalent to 15.8 per cent of the total calories, milk 31.8 per cent, vegetables and fruit 17.8 per cent, fats 18.1 per cent, meat, eggs, cheese etc., 11.4 per cent, sugars and sweets, 5.6 per cent, all expressed in the proportion of the total daily calories each item supplied. The average intake of calcium and of phosphorus was 1.4 and 1.5 gm., respectively. A second and third diet differed from this one in that sugar was added in amounts sufficient to increase the total calories by 6 per cent and sixteen to eighteen per cent, respectively. On the low sugar diet the average retentions of nitrogen, calcium and phosphorus were 26, 5 and 7 mg per kilogram of body weight per day. The second diet gave retentions practically the same as these, while with the high sugar intake there was reduction in the retention of calcium in five out of seven girls studied and a tendency to increased retention of nitrogen and of phosphorus. The retention levels observed in this study are lower than those considered desirable by some students of mineral metabolism.

Stearns³⁵ reported in abstract the summary of retentions of calcium by infants and children receiving various amounts of milk, with diets which otherwise were quite comparable. The infants and young children were given additional vitamin D. The age range included children from six weeks to twelve years. The infants retained as much or more total calcium than the older children for any given amount ingested. The lowest level of retention was in the group aged three to five years. The retention per unit of body weight was highest in early infancy, declining during infancy and early childhood. In all cases, higher retentions were

obtained when the intake was increased. The curves of daily retention levels per unit of weight plotted against the age of the subject paralleled closely the predicted curve of yearly increment in height.

In a study of the relative value of a pint as compared with a quart of milk a day in the child's diet, Daniels and her coworkers³⁰ determined the retentions of calcium, phosphorus, and nitrogen in children of pre-school age on the two levels of calcium intake as supplied by those amounts of milk. They noted a wide variation in the amounts retained by children of the same age, and by the same child, when the two intakes were employed. Those children previously well fed retained less than those who initially had lower reserves of nutrition. They suggest that the physiologic condition of the children at the time of the test and their individual potentialities for growth apparently condition the wide variations noted in the retentions. However, they conclude that when the diet supplies sufficient protein, phosphorus, and vitamins from other sources, a child between the ages of three and five years can obtain sufficient calcium for its needs from a pint of milk daily. The retentions noted were 3 to 10 mg of calcium, 6 to 8 mg phosphorus, and 34 to 90 mg nitrogen per kilogram per day.

Porter-Levin³⁷ observed retentions varying from 8 to 17 mg calcium and 5 to 8 mg phosphorus per kilogram body weight per day in children of similar age.

Boyd, Dрам, and Stearns³⁸ correlated the retentions of children who had dental examinations made simultaneously, many children being re-examined on several subsequent occasions. All received diets high in the various protective factors. Correlations showed that highest retentions of calcium and of phosphorus were noted among the children whose teeth were free from decay, intermediate retentions in those whose teeth showed inactive decay, and least in those with active decay. The latter values, however, were as high as or higher than those usually accepted as normal, while those of the children with no caries had retentions averaging approximately 50 per cent higher than the group with active caries. The investigators question whether the usually accepted retention values may not be considerably less than the optimum.

The gap between familiarity with the nutritional needs of the body and the application of this knowledge to the practical feeding of children is not a great one. The factors involved include the availability of the various essentials in common and readily obtainable foods and the ability of parents to supply them and to administer them to the children in a suitable manner.

If attention is paid to the use of foods high in their content of protective factors, such as qualitatively valuable protein, calcium, and the various vitamins, the energy relationships usually need little consideration. Foods of the type mentioned include milk and its products, eggs, fruits and vegetables in variety and in liberality, and cod liver oil. While the latter may be omitted with safety when the diet otherwise is liberal, it enhances the value of a good diet and lessens the dangers of the limited diet. Morse³⁹ has recently reviewed the necessary requirements in a minimum diet for infants and children. While such limitations may be economically necessary, outstanding advantages are offered by the diet which is high in the various essentials for nutrition. While meats are desirable and advantageous in the child's diet, they should not be used to replace milk or other foods. Sherman¹ emphasizes that

grains are still the staff of life, and that if only a very moderate proportion of these is consumed as "whole," or slightly milled, the intakes of phosphorus, iron, copper, manganese, and vitamins B and E will usually be ample. Milk, fruit, vegetables, and eggs will meet the needs for calcium, phosphorus, and for vitamins A, C, and G easily, agreeably and economically if eaten in moderately high percentage in the diet.

The economic aspects of adequate nutrition are of great importance at this time. An English authority² estimates that in England at present prices the minimal safe diet for an adult will cost \$1.25 per week for raw food, and that for a young child the cost will be 75 cents. Desirable diets will cost correspondingly more. Because of this, he states that in certain communities adequate diets cannot be obtained. Yet much of the difficulty lies in the manner in which the money for food is spent. Hawley,³ in an attempt to compromise between the limitation of money for food and the needs of the body, has suggested the following as a safe diet, approaching a minimal cost for safety: milk—2 to 4 cups as such for each child daily, one cup for each adult, one milk dish daily for the entire family, cereal—daily for breakfast and in some form again during the day, one of these should be as whole grain, fruit—three times weekly, dried prunes, peaches or apricots once a week, potatoes—usually once a day, or oftener if desired, vegetables—two daily, as soup or as salad, tomato—daily for children, three times a week for adults, eggs—two or three a week for very small children, daily for those over two years if possible, legumes—once a week, cheese, fish—once a week, butter—once daily, the remainder of table fat may be served as oleo-margarine, meats—two to three times a week, daily if desired and if possible, liver, heart or kidney should be served once a week, cod liver oil—daily for all preschool children for all who are underweight for those on special diets, and when prescribed by the physician. Through aid in food budgeting and through the aid given by relief agencies, the health and nutrition of these children so supervised have been reported to be at higher levels than heretofore.

Among the more favored economic groups, the problem of wisdom in choice of food frequently is as assertive as among the poorer classes. In addition, the psychologic aspects of child feeding are decidedly more in evidence in the former than in the latter group. Hunger strikes, poor appetite or anorexia, and similar difficulties often outweigh all other phases of the practice of nutrition with these children. No agreement exists as to the best measure for correcting these psychologic barriers to good nutrition. Such attitudes may be credited to the attitudes of the other members of the household, and if this and other aspects of the environment could be made ideal, much of the difficulty would be prevented. Contributing factors in the mental set of the child toward his food include the example as to eating offered by the other members of the household, differences of opinion concerning food needs, outstanding and loudly expressed dislikes for certain foods, the desire of the child to assert himself through his food habits or to gain his share of attention in the table conversation, the overzealous and often misguided efforts of the mother to make the child eat. Certainly it is most essential that the eating of suitable food be made a matter of course, and one devoid of emotion or display of force. The manner of attack is the question to be answered. Many proponents urge that the diet of the child be left to his free choice and data have been presented in the foregoing

to show that such a regimen may be nutritionally satisfactory. Various studies of the quality and quantity of food ingested under free choice have been published, with more or less critical attitude on the parts of their authors as to the adequacy of the diets chosen. Aldrich¹³ states that the normal child will eat enough food for adequate nutrition if it is offered to him in an intelligent manner, in an attractive form, and without undue urging and that the properly handled average child of twelve to eighteen months should be able to feed himself all important foods. Once this is accomplished, the child should be left to his own responsibility regarding his feeding, without suggestions as to the type or amount of food, or the speed of eating. Solitude may lead to anorexia with negativism to the intake of the foods most urged, which usually will be those considered the most important. However, the crux of the whole system is the offering of only those foods which are qualitatively adequate. In other words, for such a regimen to succeed, the parents must have greater insight than usually is displayed concerning the types of foods of value in nutrition, the child should eat under conditions free from distractions, in a pleasant environment. The child must not be credited with any uncanny ability to sense his nutritional requirements. Harris⁹ reminds us that the baby with rickets has no instinctive craving for cod liver oil, the high incidence of evidence of rickets throughout most of the northern climates speaks against the safety of a self-choice regimen. The same investigator has studied the instinctive ability of animals to choose their own diets wisely and has found that only when a change in diet is immediately beneficial will a rat adopt a desirable change. He states that correct nutrition cannot safely be left to instinct, or to the use of "natural unspoiled foods," or to a varied diet, or to a process of free selection. Some form of desirable motivation is necessary to direct the child into suitable habits of diet. Hamill¹⁴ expresses his opinion that the nature of a self-selected diet will be dictated by the appetite rather than by the immediate physiologic needs. While life undoubtedly would continue on a self-choice type of dietary, as it has done for countless generations, the safety of such a regimen will be in relation to the intellectual and economic adequacy of those administering it, moreover, the conscious improvement of the level of health which designed nutrition permits will not be achieved readily, if at all, under such conditions.

The answer seems rather to lie in the dissemination of ideas concerning the interdependence of radiant health and the nature of the food intake, and the relative values of various foods. Then, if the whole household will consider food as a physiologic necessity rather than merely a means for pleasing the appetite, a compromise may be effected between the free choice of a diet from the substances wisely offered and the wise supervision of the whole dietary. The success of such a regimen is exemplified in those children who because of diabetes mellitus are placed on a rigid form of diet, complete in all regards, and who, having adjusted themselves mentally to such discipline, enjoy the regimen and exhibit a nutritional state which is superior to that of their brothers and sisters whose nutrition is left to their own direction.

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Round Table Conference on Syphilis

Leader Dr Joseph Yampolsky, Atlanta, Ga Assistants Dr M Hines Roberts, Atlanta, Ga, and Dr Lemuel R Brigman, Cleveland, Ohio

The Round Table Conference on Syphilis held at the Wade Park Manor Hotel, Cleveland, was called to order by Dr Joseph Yampolsky, chairman.

CHAIRMAN YAMPOLSKY—This discussion will take up the treatment of syphilis in children. Dr Roberts will speak on "The Transmission, Occurrence, and Behavior of Congenital Syphilis," with emphasis on the treatment. Dr Brigman will discuss "The Untoward Effects of the Use of Arsenicals in Children," and I will discuss the many and various preparations used in the treatment of this disease

Treatment of Syphilis in Children With Special Emphasis on the Use of Stovarsol Joseph Yampolsky, M.D

Today syphilis in children is more easily recognizable, therefore, more cases are seen and are amenable to treatment. This is true especially in children born of known syphilitic mothers, without the children themselves manifesting symptoms of syphilis or in those whose diagnosis is assured only through a positive Wassermann reaction.

Starr¹ in his textbook, *Diseases of Children*, as early as 1894 stated that the treatment of hereditary syphilis must be conducted in accordance with those principles which govern the therapy of acquired syphilis in adults with such modifications as are demanded by the age of the patient. The treatment at that time consisted primarily of the use of mercury and iodides in one form or another. As late as 1924, Veeder² in Abt's *Pediatrics* stated that three drugs are in common use in the treatment of syphilis in children, viz, arsphenamine products, mercury or one of its salts, and potassium iodide. However, drugs are constantly added to our armamentarium in the treatment of this disease. At present besides those mentioned, two new drugs in the form of bismuth and stovarsol have been added and also the infrequent use of a combination of bismuth and arsenical preparations in the form of bismarsen.

In outlining the treatment of syphilis, we might consider Wegner's³ general rule in application of medications used. The treatment depends on the following formula

1. The variety of the clinical symptoms and their percentilo distribution over various ages (infancy up to the age of one year, young children from 2 to 5 years, school age from 6 to 13 years, adults over 14 years of age)
2. The effect of the treatment in the various ages.
3. The results in the cases which became negative and in which the follow up examination revealed negative clinical and serologic pictures.
4. The fate of the patients who did not become negative in spite of the 'chronic,' continuous treatment
5. The duration of the treatment

Arsenical Drugs

The most common arsenical drugs used are arsphenamine and neoarsphenamine. While the weight of evidence is in favor of arsphenamine, neoarsphenamine is more useful in children because of the ease of administration.

Neoarsphenamine.—Neoarsphenamine does not have to be neutralized and may be given intramuscularly with safety, one-half dose can be given in each hip with little pain and little chance of abscess formation. It is given deeply but not under the aponeurosis. It is given in the upper part of the buttocks or external surface of the thigh. Two injections are made each week with a total of fifteen injections.

The following method of treatment in a case of syphilis has been used at Emory University School of Medicine. A course of sixteen injections of neoarsphenamine alternating weekly with mercury salicylate or bismuth is given. The dosage is 0.02 gm. of neoarsphenamine dissolved in 0.4 c.c. (six minims) of freshly distilled sterilized water given either intravenously or intramuscularly for every 3 pounds of body weight. When the intramuscular injection is used, one-half of the dosage is given in each buttock and hot compresses are applied to the buttocks for one-half hour after the treatment. Mercury is given in the form of a suspension of mercury salicylate in olive oil or cold cream intramuscularly and the dosage is 0.5 grain to 30 pounds of body weight. After the sixteen weeks of treatment a thirty day rest is given when the Wassermann test is made. If the Wassermann reaction is negative, the patient rests for sixty more days and then a complete course of treatment is given again. If the Wassermann reaction is positive, a complete course is begun immediately, but mercury is omitted completely and bismuth used instead. No more treatment is given during the first year of observation. After the second course an examination of the spinal fluid is made. Wassermann reactions become reversible when treatment is begun very early in infancy and especially in those who have positive serologic reactions only. Later in life it is difficult to reverse the Wassermann reaction.

Arsphenamine.—Arsphenamine should never be used intramuscularly. Silver arsphenamine has not been employed very much in the treatment of congenital syphilis, and even in adults it is used more often in neurosyphilis. Sulpharsphenamine may be used in children over five years of age because of the ease of administration and the absence of after-effects. In the cases in which treatment was instituted early, the greatest number of cures were obtained. Serologic reverses were obtained in practically all children under five years who stayed for at least one year's treatment. When treatment was inaugurated at a later age the response became less satisfactory as the age of the patient advanced. In the older cases mercury and the arsenicals are needed over so much longer a period of time that one must consider the toxicity of the drugs as well as the disease itself. Slow arsenic and mercury poisoning must at least be kept in mind in cases in which treatment is necessary over a long period of time. When arsphenamine is used by the syringe method, it may be diluted in as little as 0.1 gm. in 4 c.c. of water. A safe dilution of the neoarsphenamines is about 0.1 gm. to 2 c.c. of cold freshly distilled, sterilized water.

Intraperitoneal Method—The use of neosarsphenamine intraperitoneally is worthy of trial if difficulty is found in injecting arsenicals intravenously and if syphilitic manifestations are so acute that a method must be found for the quick absorption. We have reported a study of seventeen cases. Before starting treatment on the children, we injected several rabbits intraperitoneally, giving 0.02 gm of neosarsphenamine for every 3 pounds of body weight diluted in 0.4 cc (6 minims) of freshly distilled, sterilized water for a full course of treatment. No bad results were encountered at any time. After many months an autopsy was performed, and there were no signs of adhesions or peritonitis. Some of these rabbits were submitted to autopsy shortly after the injection of the drug. The absorption was almost immediate, and the peritoneum was glistening and normal in every way. After a full course of treatment for the children a gastrointestinal x-ray examination was made on the first two patients. No ill effects were noticed along the whole intestinal tract, and no adhesions were present.

We present the following summary:

1. In seventeen cases of congenital syphilis covering a period of over four years, patients were given from sixteen to thirty-two intraperitoneal treatments, and in one case, eight. Only four of these patients present positive Wassermann reactions after treatment, but no patients present any signs of congenital syphilis.

2. Both neosalvarsan and mercurosal were given intraperitoneally, these caused no deaths, no peritonitis, or adhesions, as shown by experiments on rabbits. There was no bad effect on human beings as shown by x-ray and fluoroscopic examination.

3. Absorption is rapid from the peritoneal cavity, and if the injection is made with proper aseptic technique, it should be attended by no bad sequelae.

Mercury

Mercury is the oldest preparation used for the treatment of congenital syphilis. Mercury salicylate has been used extensively, 0.5 grain for every 30 pounds of body weight can be given intramuscularly. Another preparation, bichloride of mercury, can be given either by intramuscular injection, the dosage being 0.033 cc of a 1 per cent solution per kilogram of body weight or by mouth in the form of gray powder, the dosage being 0.2 grain twice daily to infants up to 2 grains three times daily in older children. The ease with which the veins may be sclerosed should keep us from resorting to the intravenous use of mercury. Mercury has been used byunctions in very young infants. This is usually given in the form of mercurial ointment. The dose is from 15 grains up to 1 dram. Theunctions are given in different parts of the body to avoid irritation. Mercury may also be given to the lactating mother as a safe and accessory form of treatment. The use by inhalation of mercury is of no value.

Bismuth

Bismuth has been used with success in both acquired and congenital syphilis. The summary of Sutton⁶ is most interesting. He said that bismuth seems especially useful for patients who become intolerant to arsenicals when one cannot resort to mercury. In old, treated syphilis the field of action of bismuth is applicable because of its breadth—because arsenic becomes devoid of action and is poorly tolerated as a result of a sensitization on the order of anaphylaxis which develops.

It is advisable to use bismuth intramuscularly and not intravenously. Oral and dental examinations should be made constantly during this course of treatment, and a urinary examination should be made for the presence of albumin.

Quinodibismuth is one of the valuable compounds of bismuth. The others contain more bismuth, but the addition of quinine and iodide reinforces its action. The soluble salts, permit precise dosage, a greater absorption, and a regular action. Its efficiency is equivalent to that of the insoluble salts but necessitates a greater fre-

quency of injections because of the rapid elimination of bismuth. The most common salts used in this country are salicylate of bismuth, bismuth sodium tartrate, and quiniodobismuth.

The Council on Pharmacy has warned against the intravenous injection of bismuth salts, and it would seem that, when a preparation can be given into the muscles, its intravenous injection would expose the patient to needless risk. Nitritoid crises have been reported following the intravenous injection of soluble bismuth compounds, and cases of sudden death have occurred when an insoluble suspension was injected accidentally into the circulation.

Bismarsen

The most comprehensive study of the use of bismarsen in children has been reported by Chambers and Koetter.¹ These authors used bismarsen in 180 children and infants observed for periods varying from one to two and one-half years. A total of 6,349 injections have been given to date. The ages varied from birth to fourteen years of age, the majority being three years old.

A complete serologic reversal occurred in 51 per cent. In 41 per cent the reaction remained unchanged, 8 per cent showed ultimate reversal. The Wassermann reversal occurred by the tenth week in 4 per cent, by the twentieth week in 25 per cent and by the fortieth week in 41 per cent. No relapse occurred in any other clinical form except in interstitial keratitis.

Iodides

The iodides should be used only in cases of late hereditary syphilis since they have little effect upon the *Treponema pallidum* but may be useful in aiding the absorption of exudative gummatous processes. The drug is not well tolerated by nurallings and often causes a coryza which interferes with nursing. Potassium or sodium iodide is usually used, and the dosage from 0.2 to 0.05 gm.

Stovarsol

The experimental use of stovarsol in spirochetal and trypanosomic infections was first published by Fournier in 1921. This preparation is also known as 'acetarsone' or 'spirocid' by the Germans. Stovarsol contains from 27.1 to 27.4 per cent of arsenic and is chemically known as acetylanilinohydroxyphenylarsonic acid. It is furnished in 0.1 gm. and 0.25 gm. tablets. A 0.25 gm. tablet contains approximately 0.0068 gm. of arsenic while an 0.1 gm. tablet contains approximately 0.0027 gm. of arsenic.

The medication may be administered as outlined in Table I.

TABLE I

PERIOD	DURATION OF PERIOD	DOSE OF STOVARSOL DAILY PER EQ.
First	7 days	0.005 gm. $\frac{1}{32}$ grain
Second	7 days	0.010 gm. $\frac{1}{16}$ grain
Third	7 days	0.015 gm. $\frac{1}{8}$ grain
Fourth	7 days	0.02 gm. $\frac{1}{4}$ grain
Fifth	5 weeks (5th, 6th, 7th 8th 9th weeks)	0.02 gm. $\frac{1}{4}$ grain
Sixth	6 weeks	none (rest for 6 weeks)
Duration of entire active course		9 weeks
Duration of rest period		6 weeks

If the Wassermann reaction is positive, no rest period is given, treatment is begun with usual dosages during the first week, to be continued for nine weeks as shown in Table I.

Some authors claim that it is best to administer one dose daily. We have used the daily dose divided into three equal parts given in milk or water one half hour before meals. Since stovarsol is rapidly decomposed in an acid medium free arsenic is liberated to be rapidly absorbed in the body.

The reactions to the use of stovarsol may be summarized as follows

- 1 Eruption of a scaly nature over the body
- 2 Diarrhea
- 3 Hypertrophia
- 4 Pyuria
- 5 Nephritis
- 6 Death

Other authors report Herxheimer's reaction and albuminuria. The medication should be discontinued at the first signs of sensitivity to the drug, though in a short while treatment may be resumed.

Our routine treatment is as follows

- 1 Wassermann reaction is taken before and after treatment
- 2 Complete blood examination is made when possible before and after treatment
- 3 X ray examination is made of all long bones and of fingers and toes before and after treatment
- 4 Urine specimen at least twice during treatment is collected and examined macroscopically and microscopically
- 5 Temperatures are taken only if there is some suspicion of fever
- 6 Weight is recorded on every visit to the clinic
- 7 Spinal puncture is performed, and Wassermann test and globulin and cell count are made on spinal fluid in every case at the end of the treatment

The results of the Wassermann tests are reported in Table II, urine examinations

TABLE II

NO	BEFORE TREATMENT		MOTHER'S WASS	AFTER TREATMENT	
	AGE	BLOOD WASS		BLOOD WASS	SP. FLUID WASS
153746	7 wk	++++	neg		
155678	8 wk	++++	neg	++	neg
1--020	8 wk	++++		neg	neg
151187	11 mo	++++	++++	++++	neg
153011	18 mo	+++		neg	neg
146806	19 mo	6/15/32 neg 10/ 7/32 +++++ Wass fast +++++		++++	neg
153036	3 yr			neg	
152607	3 yr	++++		neg	neg
119145	5 yr	++++		++++	neg
151159	7 yr	8/ 9/32 neg 8/22/32 +++++			
150645	8 yr	1925-----++++ 1933-----++++		neg	neg
135845	9 yr	++++			
119136	10 yr	Wass fast		++++	neg
148421	10 yr	++++		++++	
153087	11 yr	++++		++++	neg
154114	11 yr	++++		++++	neg

were negative in all cases except one in which there was transitional pyuria. blood counts are reported in Table III, clinical findings, in Table IV. x-ray findings in Table V.

TABLE III

AGE	BEFORE TREATMENT			AFTER TREATMENT		
	HGB %	R.B.C.	FOH. %	HGB %	R.B.C.	FOH. %
7 wk.	50	2 plus	5	60	3 plus	3
8 wk.	66	3 plus	-	61	3 plus	1
8 wk.	66	3 plus	-	61	3 plus	3
11 mo.	55	3 plus	-	61	2 plus	-
18 mo.	53	4 plus	1	67	3 plus	-
10 mo.	66	3 plus	-	60	3 plus	-
3 yr.	65	3 plus	2	-	-	-
3 yr.	80	4 plus	3	-	-	-
5 yr.	80	4 plus	4	70	3 plus	-
7 yr.	60	4 plus	4	-	-	-
8 yr.	-	-	-	75	4 plus	-
10 yr.	73	4 plus	6	-	-	-
10 yr.	80	4 plus	-	83	3 plus	2
10 yr.	90	5 plus	7	-	-	-
11 yr.	80	5 plus	-	83	3 plus	-
11 yr.	80	4 plus	2	83	4 plus	-

TABLE IV
CLINICAL FINDINGS

AGE	BEFORE TREATMENT	AFTER TREATMENT
7 wk.	Painful swelling of thighs and knees	Improvement in ability to use legs
8 wk.	Peeling of palms and soles and inability to use limbs	Able to use arms and legs. skin lesions improved
8 wk.	Swelling and tenderness right elbow	Improved
11 mo.	Snuffles, malnutrition	Improved
18 mo.	Anal condyloma	Improved
10 mo.	Palpable cervical lymph nodes, malnutrition	Improved
3 yr.	Maculopapular rash on trunk and extremities	Improved
3 yr.	Vulval condyloma, palpable cervical glands	Glands improved. condyloma improved
1 yr.	Snuffles with nasal swelling	Slightly improved
7 yr.	Interstitial keratitis, buritis, both knees	Improved
8 yr.	In 1925 epiphysealitis right femur, no treatment in 1933 swelling and pain in both knees	No improvement until after 7 wk. of treatment
9 yr.	Cervical adenitis	Marked improvement
10 yr.	Generalized adenopathy 1929 Wass. fast 1933	No improvement
10 yr.	Swelling left knee no pain	Improved
11 yr.	Keratitis perforation in roof of mouth. snuffles	Keratitis improved greatly. snuffles disappeared
11 yr.	keratitis	After 2 courses of treatment very little improvement

Our conclusions are as follows. Oral treatment of syphilitic children is coming back into use because of the advantage of such medication. Although negro children show very little toxicity to this drug it is important not to use the medication indiscriminately. The disappearance of skin lesions and the general improvement of the patients make us feel favorably disposed to the use of stovarsol.

TABLE V
X RAY FINDINGS*

AGE	BEFORE TREATMENT	AFTER TREATMENT
7 wk	Periosteal thickening of long bones, increased density of epiphyses	
8 wk	Slight destruction upper ends of both ulnas, lower end right radius	Definite periostitis in bones of lower extremities, improved left elbow
8 wk	Periosteal thickening upper end of right ulna	Improvement in long bone lesions
11 mo	Periosteal thickening of long bones, increased density at diaphyses	No material changes observed
18 mo	Diaphyseal erosion, cross sections of increased density in femurs	Nearer normal density, slight erosion at lower ends of both tibia
19 mo	Bone destruction both ends of bones of forearms, syphilitic osteomyelitis	Not obtained
3 yr	Erosion of lower epiphyses of femurs, periosteal thickening of radii	Not reported
3 yr	Expansion of diaphyses of long bones	No change in bone lesions
5 yr	Periosteal thickening of margins of long bones	No definite changes
8 yr	Epiphyseal separation of lower end of right femur	No definite evidence of syphilitic involvement
9 yr	Slight periostitis along shaft of left radius at wrist	Not reported
10 yr	Marked periostitis of both tibia and fibula	Tibiae slightly sabered Periosteal reaction anterior border of left ulna
11 yr	Periosteal thickening at lower end of femurs	Periostitis lower end of diaphyses both femurs, progressive syphilis

*Three cases were negative before and after treatment.

This is also true in the serologic reactions, and especially in our cases of the reversal of the Wassermann reactions in the Wassermann fast cases. The roentgenologic results have not been gratifying. The status of stovarsol is still not definitely known. We do not believe that this drug per se without the use of other medications can cure syphilitic lesions of bones and many other late lesions of congenital syphilis, but we certainly agree with other writers that stovarsol has a definite place in the treatment of this disease.

Treatment of Neurosyphilis

If after a year's duration of the ordinary antisyphilitic treatment the patient still has signs of neurosyphilis, it is advisable to use intraspinal treatment, though in our experience treatment has not been successful. We wish to describe the injection of arsphenaminized serum in neurosyphilis. One-half hour after the intravenous injection of the arsphenamine, serum is obtained from the blood and from 10 to 25 cc (according to the size of the child) is given intraspinaly. This serum may be inactivated at 56° C for one half hour in order to increase the efficacy of the drug. The same amount of spinal fluid is then withdrawn and the serum is injected into the spinal canal. Occasionally the arsphenaminized serum may be further fortified by the addition of arsphenamine before injecting it into the spinal canal. Veeder² occasionally adds 1 or 2 mg of mercuriochloride before inactivation.

Solomon and Epstein⁸ inject hypertonin solutions of saline intravenously six hours before the injection of the arsenical preparations through the same route. A spinal fluid examination reveals that the arsenical content is much increased in these cases.

Malarial Treatment

The use of this treatment for interstitial keratitis may also be used in neurosyphilis in children, occasionally with some remission of symptoms.

Use of Tryparsamide in Treatment of Neurosyphilis

Let us report briefly an opinion of Reese¹⁰ "The disappointing response to Ehrlich's compounds, arsphenamine and neoarsphenamine in neurosyphilis has caused clinicians to take a pessimistic view. Arsphenamine changes the biology of the spirochete consequently modifies the histopathologic effects of the virus, and produces a clinical entity meager in symptoms. Without arsenical therapy a large number of the metasyphilis of today would be the tertiary syphilis of the past. We do not agree with statements in the literature that arsenical therapy alone is responsible for the increase of general paralysis and tabes dorsalis. The steadily increasing curve of general paralysis for both sexes is not the result of insufficient antisyphilitic therapy but is due solely to the increase of recognized syphilis."

Tryparsamide is the sodium salt of the amide of the phenylglycino-p-arsenic acid, obtained by replacing the hydroxyl group of the carboxyl with the amide group. Tryparsamide has a very feeble spirocheticidal activity. It is inert in the first and second stages of syphilis, in syphilitic aortitis, in tabetic arthropathies, and in tertiary manifestations in general, which fact precludes its therapeutical use in these types, but it gives best results in the meningovascular type of neurosyphilis.

The dose of tryparsamide is 0.04 gm. per kilogram of body weight that is, an average of 3.0 gm. in adults or 2.0 gm. in small children. Tryparsamide must be used over a period of months and years and cannot be judged by the effect of one two or three courses. The addition of mercury results in more permanent improvement of the serologic findings, as well as a more rapid and prolonged clinical benefit. As a practical routine, we recommend from eight to sixteen injections to be given at weekly intervals, combined with mercury or bismuth preparations. Tryparsamide medication is followed by a decided gain in weight and by improvement in the physical condition, indicating a great stimulative effect upon the general metabolism. If a patient under tryparsamide treatment does not gain in weight, the prognostic outlook is doubtful, if not poor.

There is general agreement that the effect on the pleocytosis is prompt.

A summary of our serologic results reveals

Blood Wassermann	40.2% negative
	35.5% reduced
	15.2% unchanged positive
Spinal fluid Wassermann	25.7% negative
	47.0% reduced
	37.3% unchanged positive

The statement referred to in all reports that tryparsamide is a menace to the optic nerve, causing toxic amblyopia, necessitates comment. If careful examinations of the eyes are made before and during treatment most of the ill effects can be avoided.

CONCLUSIONS

Apparently many drugs are used in the treatment of syphilis in children. Many methods have been described for consideration.

The problems for discussion should be as follows

- 1 What drugs are most effective in the use of the different stages of congenital syphilis?
- 2 What method of procedure is to be employed in deciding the length of treatment?
- 3 Should arsenicals be used without the aid of metallic salts? This is of especial importance in the use of stovarsol
- 4 How long should one wait before treatment is given to a child born of a syphilitic mother although the child is clinically and serologically negative at birth?

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DISCUSSION

DR BRIGMAN—Can you reverse the Wassermann reaction when it remains positive under stovarsol by using salvarsan with mercury or salvarsan with bismuth? I have given stovarsol in old treated cases rather than in the untreated cases. I have found a number of Wassermann fast cases which after one or two courses of stovarsol showed a reversed Wassermann reaction. I have had no ill effects from stovarsol except mild diarrhea, which disappeared on stopping the drug, and one or two cases of mild pruritus.

Skin lesions disappear after stovarsol almost the same as after salvarsan, arsenic, and bismuth, but the bone changes do not disappear as rapidly. This suggests that stovarsol has a greater effect on skin syphilis than on bone syphilis.

I have just started a new plan. In other words, what I tried to do, instead of giving the rest period according to the Bratusch-Marrain outline and then another course, I follow the two courses concurrently and have doubled the time, which gives a longer treatment without ill effects from the drug. Whether the Wassermann reaction becomes negative sooner, I do not know.

CHAIRMAN YAMPOLSKY—Do any of you give arsenical drugs gradually in syphilis in children?

DR E G PADFIELD (SALINA, KAN.)—I have seen cases of keratitis treated by combined therapy with fairly satisfactory results, a few were not so good, but they were apparently better than were reported from stovarsol. I have been wondering if we are coming back to our old treatment of keratitis, considering the results which are obtained from stovarsol.

CHAIRMAN YAMPOLSKY—The question of rest is important. Some authors agree we should have a rest period, and others think a rest period is not wise. In an older person we usually give iodides, but they are of no benefit in young children, especially in sucklings.

DR BRIGMAN—I alternate the treatment of my cases, one gets bismuth and the next salvarsan, neosalvarsan, or sulpharsphenamine. The next patient will get

bismuth and salvarsan, and the next one, stovarsol so that we have at the same time a group of patients who will show about the same results. We will learn more from our results than from mapping out an objective and then trying to reach it by some particular form of treatment.

We had an opportunity to study congenital syphilis in a very large number of patients, and have become interested in the transmission of the disease and its development. It has so many peculiar phases and apparently many controversial methods of behavior. The very name of the disease (whether it is hereditary or congenital) has been in controversy for many years. At the old Babies Hospital we made a careful examination of the patients whose history suggested syphilis and we found 3 per cent with a positive Wassermann reaction. This group was made up mostly of colored infants and a few of foreign parentage. However when we took a Wassermann reaction of every patient regardless of what or who he was, our percentage increased about 1 to 1.5 per cent so that 3 per cent was a general average.

DR. ROBERTS—In our present studies the incidence of positive reactions is going to be somewhere around 5 per cent.

DR. W. I. McDOWELL (Norfolk Va.)—Ours is 7.5 per cent in an unselected group of patients, 6, per cent of whom are negroes.

DR. ROBERTS—I should think the incidence among the negroes, exclusively would be around 7 per cent. Would you expect it to be higher in infants than in older children?

DR. McDOWELL—Our figures are rather high compared with the figures that have been given.

DR. ROBERTS.—We have observed twenty-eight babies who never showed syphilitic disease and who had positive blood tests which within three or four years became negative. Such a positive Wassermann reaction is probably due to the fact that the reacting substance in the mother's blood is transferred to the baby's blood for a short time and then disappears.

The Transmission Occurrence and Behavior of Congenital Syphilis M. Hines Roberts, M.D.

The capricious behavior of the syphilitic infection in man, with its many apparently contradictory phases, stands as a constant challenge to the investigative mind. In no phase of the infection is this so strikingly evident as in so called congenital syphilis. Even the name of this phase has been the center of controversy for the implications of hereditary as opposed to congenital syphilis are of such importance as to influence our entire concept of the infection.

Two schools of thought have arisen as to the mode of infection, namely transmission through germ cell—hereditary syphilis—and transmission by way of the placenta or birth canal—congenital syphilis. The obscure behavior of the infection accounts for this controversy. The appearance of syphilis in the offspring of a woman apparently free of the infection from the standpoint of history and physical or serologic evidence has made the diagnosis of congenital syphilis difficult of explanation. The fact that the spirochete is many times larger than the spermatozoon seems to make the theory of germ cell transmission physically impossible. These and other apparently contradictory phenomena have accentuated the argument.

Advocates of germ cell transmission hold that the spirochete is pleomorphic, that during certain stages of its life cycle it may exist as an intramicroscopic granular body easily harbored by the spermatozoon. Certain work advanced by Burget and others seems to confirm this theory. Hochsinger claims undoubted paternal transmission in several cases followed in private practice for many years.

The apparent inconsistency of the normal healthy mother bearing a syphilitic child is explained by the group upholding placental transmission by the fact that syphilis may frequently pass through a latent or occult phase, during which the infection cannot be proved. This is especially true during pregnancy. It is fairly common observation that pregnancy appears to confer a certain immunity to the ravages of the spirochete. This may be seen not only in the recession of physical findings, but also in the reversal of the Wassermann reaction. It is believed, however, that these patients, if watched carefully over a sufficient period of time will invariably present clinical or serologic evidence of the disease.

As more data have been submitted, investigators in this field lean more and more to the theory of placental transmission of the disease. In his *Modern Clinical Syphilology* Stokes summarized as follows: "Most observers accept the maternal transmission of syphilis as the usual, if not the invariable, mechanism. They remain, however, open minded to the possibility of a rest form of spirochete discovery of which may ultimately establish the possibility of paternal transmission. There can be no doubt that one meets from time to time clinical cases in which maternal transmission is, to say the least, obscure."

Moore, in his recent work on syphilitic therapy, reached a similar conclusion.

The incidence of syphilis in children is most difficult to determine accurately. Statistics vary widely, depending on the source of the material—whether hospital, out patient, or private practice—whether cases have been studied intensively for this disease—whether the statistics are taken from a large unselected group.

Jeans and Cooke, in their excellent monograph, stated that hospital clientele of this country shows a syphilitic incidence among children varying from 2 to 35 per cent. If the age of patient is considered, it is found that the older the child the lower the syphilitic incidence, a fact probably accounted for by the higher mortality rates in the syphilitic group.

These authors report their findings in 62,815 children admitted to their out patient service in St. Louis, over a period of thirteen years. Of this group of children, 1,202 were recognized as syphilitic, 1.9 per cent.

Since the incidence of syphilis in childhood is highest in infancy, Jeans and Cooke attempted a study of the infant population of St. Louis. They found that 15 per cent of negro infants were syphilitic at the time of birth, while 1.8 per cent of the white babies showed the infection. They concluded further that 2.8 per cent of all babies born in St. Louis were syphilitic.

It is of interest to compare these figures with the incidence of syphilis among pregnant women. Large maternity hospitals with varying races and varying economic groups present a figure varying from 5 to 8 per cent. In the studies of McCord and others syphilis occurs in about 20 per cent of pregnant negro women.

The discrepancy in the incidence of syphilis noted in the newborn as compared to what is observed in the pregnant woman is explained by two factors: first, the influence of prenatal therapy on the product of conception, and second, the natural escape of a certain percentage of infants born of syphilitic mothers.

It has been conclusively proved that adequate prenatal therapy will practically stamp out congenital syphilis. Carrying this premise to its logical conclusion, we may assume that in time congenital syphilis may become as rare as smallpox, or as we hope diphtheria will be. The tremendous problem is early diagnosis, adequate treatment, and efficient follow up.

One has but to peruse casually the literature on the value of prenatal antisyphilitic therapy to realize that here is the complete answer to the problem of congenital syphilis.

A study made by Laurent and prepared for distribution by the American Social Hygiene Association shows strikingly the effect of antisyphilitic therapy in 213

women. The first 563 pregnancies occurred before these women received treatment, the last 161 occurred after treatment.

TABLE I

	NO OF PREG- NANCIES	MACERATED FETUSES	STILLBORN FETUSES	MISCAR- IAGES	DEAD BEFORE 3 MONTHS	ALIVE AT 3 MONTHS
Untreated	563	150		33.74	24.68	26.46
Treated	161	04	5	2.5		91.87

McCord's figures among the negroes are equally illuminating. In his untreated group pregnancy ended disastrously in 66.2 per cent of the cases, in his treated group, in only 6 per cent of the cases.

In collaboration with McCord I have studied approximately 1,000 infants born of syphilitic mothers. These infants were observed for periods varying from a few weeks to eight years. Of 563 mothers receiving antisyphilitic therapy, only eighty one, or 17.7 per cent, produced syphilitic offspring. Of 178 mothers receiving nine or more injections of neocarphenamine (4 gm. or more) only ten, or 5.3 per cent produced syphilitic children, that is, antisyphilitic therapy was successful in 94.7 per cent of the cases.

Compared to these figures, there were 317 syphilitic women who received no therapy, approximately 65 per cent produced definitely syphilitic offspring.

All workers have stressed the importance of early prenatal therapy—at least by the end of the fourth month of gestation, since infection of the fetus rarely occurs before this time. The importance of this point is not to be minimized but I wish to emphasize the fact that even in the last two or three months of pregnancy treatment may be eminently successful, as was the case with a large number of our patients.

The importance of prenatal therapy in every pregnancy of a woman once proved syphilitic should be stressed. We have observed patients positive during one pregnancy, negative during another and some years later again positive. Because of the recessive tendency of syphilis during pregnancy antisyphilitic therapy should be instituted in every instance of known infection or every instance in which there is reasonable possibility of such infection.

Accurate evaluation of prenatal antisyphilitic therapy must of necessity be long and difficult. Before any dogmatic statement can be made concerning the prophylaxis of congenital syphilis, it is probably necessary to follow a large group of children to adult life. Such a study thus far has not been made. Certain facts and figures about the appearance and behavior of congenital syphilis are known however.

The observation has been made frequently that it is impossible to determine in ways with certainty the presence or absence of the infection at birth. Each of us has observed an apparently normal healthy newborn infant whose blood Wassermann reaction was negative and yet who subsequently developed clinical and serologic evidence of the disease. In a study made on approximately one thousand infants born of syphilitic mothers, 273 showed definite evidence of the infection. Of this number only 170 or 62 per cent, were so diagnosed at birth the remaining 103 developed evidence of the disease subsequently. By means of monthly physical examinations and blood tests, it was found that all babies so followed showed positive evidence of the infection by the fourth month of life, with two exceptions. In these two infants, antisyphilitic treatment was instituted before the Wassermann was rechecked. It seems probable therefore that an infant born of

a syphilitic mother and reaching the fourth month of life without physical or serologic evidence of the disease will escape the infection

What of the infant whose cord Wassermann reaction is positive, whose physical examination shows no syphilitic changes, and whose mother is definitely syphilitic? Rarely are these infants not syphilitic. We have observed some thirty odd such cases and have noted the reversal of the blood test in the first few weeks of life and the failure of these babies to develop syphilitic lesions. Other observers (recently Dunham) have observed this phenomenon and believe that probably the complement fixing substance of the mother's blood is transmitted to the infant, where it remains for a few weeks and disappears.

The so called late manifestations of congenital syphilis seem to refute the opinion expressed above—that the infant has probably escaped infection if he reaches his fourth month without evidence of the disease. Although we are unable to answer this argument with statistics it is our feeling that if these children showing "late syphilitic lesions" had been followed during the first four months of their lives, definite physical or serologic evidence of the disease would have been noted. Some of our children have been observed for eight years, and thus far this opinion still seems to hold good.

The problem of treatment of the offspring of the syphilitic mother is of tremendous importance. The statement made by many observers that all such infants should be treated, regardless of the physical and serologic findings seems unjustified in the light of present knowledge. No infant should be subjected to the ordeal of adequate antisyphilitic therapy unless its indication is certain. The baby with a negative cord Wassermann reaction and negative physical examination should not be treated but should be carefully watched. The baby with a positive cord Wassermann reaction but with a negative physical examination need not be treated if careful follow up is possible.

The positive Wassermann reaction, in the face of the negative physical findings, should be checked, and, if again positive antisyphilitic therapy should be instituted.

Of course, the positive physical and serologic cases should be treated at once.

DISCUSSION

CHAIRMAN YAMPOLSKY—Did the blood Wassermann reaction at birth differ from the cord Wassermann so that it justified discontinuance?

DR. ROBERTS—The only time it is justified is when something clouds the reaction. Anticomplementary reactions occur more frequently with this blood than sinus blood. We do not regard the cord blood Wassermann reaction as final.

DR. BRIGMAN—Clinical examinations will be a better guide in reaching a final conclusion than will the blood reaction, and the cord blood is not as reliable as blood taken from longitudinal sinus. Cord blood is unreliable for Wassermann tests.

DR. ROBERTS—The sinus blood would be just as unreliable, but your figures checked the same anticomplementary. The point is the positive Wassermann reaction does not appear always at birth but, later, from six weeks to three months, as a rule. We have never found it appearing after the fourth month. We had only two cases that failed to bear that out.

DR. McDOWELL—At what age do you take sinus blood for the first Wassermann reaction?

DR. ROBERTS.—At the end of the first month.

DR. BRIGMAN—How do you explain twins not identical, with positive blood and positive clinical syphilis in one twin and negative blood and negative physical findings in the other twin? Is it because the spirochete that is active in the mother goes through one placenta or because the placenta is possibly syphilitic in one and nonsyphilitic in the other?

I am observing two sets of twins, one child of each set being definitely syphilitic. He had every sign—positive blood reaction, physical findings, skin lesions, and so forth. The other one is a perfectly normal child and has remained so for ten years. One was syphilitic at birth and the other one was not syphilitic.

I have two other families in which the odd children are negative and the even children are positive. In the other family the reverse is true. In one family with five children, the odd ones, one three, and five, are syphilitic, two and four are not syphilitic. The other family has four children of whom the odd ones are non-syphilitic and the even ones are syphilitic.

DR. ROBERTS—This phenomenon is probably due to the presence of the syphilitic infection in the blood stream. The mothers are in a recessive stage of the disease in one pregnancy and in a florid stage of the disease in the next pregnancy. That is one of the arguments advanced against germ cell transmission. If the mother who is negative during all her pregnancies—and some workers who believe very firmly in germ cell transmission report such cases—while married to a definitely syphilitic father produces a syphilitic child, and then by a nonsyphilitic father produces a perfectly normal child of course her case makes a strong argument for paternal transmission.

DR. PADFIELD—In the case of the twins, is one justified in not treating the apparently normal child?

DR. BRIGMAN—We cannot differentiate the baby who has a positive Wassermann reaction without clinical signs from the one with both positive Wassermann reaction and signs.

DR. ROBERTS—I admit you have all the facts on your side.

CHAIRMAN YAMPOLSKY—Have you attempted to correlate the pathologic findings in the placenta with positive or negative Wassermann reactions after birth? Have you found that the placenta showed syphilitic lesions in the patients who are negative for the first month or two?

DR. ROBERTS.—I am sorry I haven't those figures. Dr. McCord has studied that point, however.

An interesting point is the question of breast feeding in these babies. I have always had the feeling we were perfectly safe in going ahead with breast feeding regardless of diagnosis. Some authors, however feel babies apparently normal, born of syphilitic mothers should never be breast fed, but the consensus of opinion is to go ahead with breast feeding regardless.

The Untoward Effects of the Use of Arsenicals in Children and Criteria of Cure in Treatment of Syphilis in Children

Lemuel R. Brigman, M.D.

Whatever the avenue of attack or the combination of therapeutic agents employed to combat syphilis, we must agree on two points: first, time and, second, continuity. It cannot be emphasized too forcefully that no time limit can be set

for the cure of syphilis. Opinion is united in a thorough and unremitting treatment over a period of years.¹

The chief factor in reducing the time period is the early diagnosis and institution of a continuous form of treatment with various combinations of drugs. Late syphilis of the central nervous system is directly related to how early treatment is started. Once the nervous system is damaged, it is doubtful if a scar can be eradicated.² To cure congenital syphilis, it is necessary to banish every clinical symptom, to reverse every positive serologic reaction, to remove every roentgenologic evidence of the disease, and to maintain this state in the patient for a minimum period of one year without treatment.

After this time it is wise to make semiannual Wassermann tests and examinations to discover cases which do not remain cured.

A positive Wassermann reaction in the newborn child is not in itself proof that the infant has congenital syphilis because this reaction may be due to antibodies passing from the mother's blood through the placenta into the infant's blood.³ Repeated tests will show a diminishing Wassermann reaction which in a few months becomes negative and stays negative if the infant does not have a spirochetal infection. Some authors advise withholding treatment to eliminate these cases from true syphilis, but it is important also not to deny the newborn the benefits of early treatment. Even without clinical or x ray evidence of syphilis, the newborn with serologic evidence of the disease is entitled to a few months' treatment until all evidence of the disease has disappeared. Kolmer describes two sources of error in the Wassermann reaction: the unavoidable or biologic, and the avoidable, or technical. This transmission from mother to infant may be unavoidable or biologic, as with yaws and frambesia, but even though the biologic action may have occurred in the mother, the positive Wassermann reaction is in the infant's blood, and, since a positive reaction is evidence of spirochetal activity, the patient must be treated.

Wassermann fast cases are often regarded as cured by syphilologists, yet we see these reactions reverse in many instances when a change of therapy is instituted.

Arsenic is an ideal treponemocide, not as toxic as bismuth, though it may cause urticaria, erythema, jaundice, pruritis, dermatitis exfoliativa, or hemorrhagic encephalitis.⁴

The arsphenamines cause about 11.2 per cent of the reactions of various kinds, the most frequent of which is a disturbance of the gastrointestinal tract resulting in vomiting and nausea in 75 per cent of these cases, nitritoid reaction, 14 per cent, and flushing and chills in about 6 per cent. Arsphenamine causes 63 per cent of the reactions, neoarsphenamine, 16.5 per cent, and sulpharsphenamine, 1 per cent. The peak of reactions come about one hour after the intravenous injections. All forms of reactions occur about one hundred times less frequently when the same drugs are given intramuscularly in children, the ideal is reached with neoarsphenamine given by the scalp method in which no systemic reaction has appeared in thirteen years of use in hundreds of patients and thousands of injections.

Ireland lists the following exanthemas: urticaria, erythema multiforme, lichen planus, herpes, keratoses, ninth day erythema, pruritis, stomatitis, hemorrhagic cutaneous manifestation, and dermatitis. All these occurred in adults following arsenobenzols intravenously. The most frequent and severe reactions result from high dosage, rapid injections, and concentrated solutions. This prevails in infants as well as in adults.

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DISCUSSION

DR. ROBERTS—Is there much pain at the time of the intracscalp injection?

DR. BRIGMAN—Apparently not very much

CHAIRMAN YAMPOLSKY—Have you not included spinal punctures in your criteria of cures?

DR. BRIGMAN—We do not, but I really believe it is a good thing to do

DR. McDOWELL—At what ages do you use the intracscalp method?

DR. BRIGMAN—Up to the time when we can make intravenous injections without difficulty, from a few days after birth to eighteen months.

The meeting was adjourned.

ANNUAL MEETING OF REGION IV OF THE AMERICAN ACADEMY OF PEDIATRICS

THE annual meeting of Region IV of the American Academy of Pediatrics was held in Oakland Calif., on October 26 and 27, 1934. Approximately forty five attended. The first session was held at the Alameda County Hospital, and the two following sessions at the Children's Hospital. Luncheon was provided at the Children's Hospital, and in the evening there was an informal dinner at the Claremont Country Club. Following the morning session on the second day a majority of the members attended the football game between Stanford University and the University of Southern California.

The program and entertainment were arranged by Dr. Clifford Sweet, of Oakland. Fourteen papers and a round table discussion of respiratory tract diseases made up the program. A few of the papers were given by invited guests. In general papers and discussions were concisely presented and found to be of interest and value. The next annual meeting will be held in Seattle, Wash. under the direction of Dr. Jay Durand.

Abstracts of the papers follow

The Treatment of Tetanus. Sumner Everingham, M.D. Oakland, Calif

Study of cases of tetanus in Highland Hospital shows an incidence of slightly more than 60 per cent occurring in children. With these figures in mind, it is essential that all wounds occurring in infected areas receive not only the usual antitetanic serum but also débridement. Once the disease has become manifest, the so-called 'healed' wounds should be searched for foreign body or necrotic material.

We also feel that in treatment of the disease the use of antitetanic serum has been used possibly too enthusiastically. Apparently the method of administration is more or less unimportant. An initial dose of forty to sixty thousand units should be administered, the effect lasting possibly for some five to seven days. Barbiturates and avertin should be used to avert spasms and convulsions and can be continued over long periods. Fluids, of course, are essential.

Bacillus Welchii Infection. D D Lum, M D, Alameda, Calif

There has been a marked increase in the incidence of gas gangrene during the past few years. Over 50 per cent of the cases are in compound fractures of the lower extremities. Prophylactic treatment should consist of immediate debridement plus the use of polyanerobic serum. The dose of polyanerobic serum should be at least doubled, as the present dosage is too small for proper prophylaxis. The usual symptoms of gangrene, subcutaneous crepitation and prostration, were enumerated. Emphasis was placed on the marked anemia due to the hemolytic action of the infection in certain cases. Treatment should consist of surgery, use of serum, and transfusion.

An Analysis of the Results in the Treatment of Pertussis With Krueger's Endo antigen. A. Lawrence Gleason, M.D., Oakland, Calif

The paper points out that Krueger's vaccine is an undenatured vaccine prepared by grinding up mass cultures of *B. pertussis* in a special ball mill machine and filtering the fragments through an acetie collodion filter. The filtrate contains the antigen. A series of 232 treated cases with 77 per cent good results using vaccine prepared in Krueger's laboratory is compared with another series showing a large percentage of poor results. The vaccine in the second series being supplied by Lilly Laboratories. It is pointed out that the latter vaccine, until the past six months, has been very spotty and uncertain. Vaccine acts by stimulating antibodies and possibly by desensitization.

Advantages No local reaction in arm, undenatured vaccine contains more antigen, helps as much in catarrhal stage as paroxysmal stage.

Disadvantages Number of doses required to obtain results.

After-Treatment of Anterior Poliomyelitis. William F Holcomb, M.D., Oakland, Calif

The after care of the paralytic patient was described in two general phases: the first or acute phase, lasting approximately from four to twelve weeks, the second phase, lasting from twelve weeks until the time the paralysis is considered static. In the discussion of the first phase were described satisfactory splints which could be simply made—the important principle being rest and the prevention of deformity. In the discussion of the second phase, the principal point stressed was the recovery of muscles based on their functional ability. It was pointed out that extreme care must be used and that the muscle should not be underexercised or overexercised. The optimum of contraction usually produces good results, whereas too much immobilization or overuse produces the same results, namely, atrophy. All strong arm methods such as violent massage, excess heat, and manipulative procedures are contra-indicated.

The Mechanism of Cellular Defense in Acute Pulmonary Diseases. James B Graesser, M.D., Oakland, Calif

Recent studies of experimentally produced pneumococcus pneumonia in dogs has afforded a more complete understanding of the mechanism of cellular defense in this disease as well as other acute pulmonary infections. The mobilization of these defenses is a methodical and rapid process. The strategy of defense in this disease, as in all infectious processes, is to localize the infection. Spread of the organisms from the original focus occurs along the alveolar walls and by growth of the organ-

isms in the serum exuded into the alveoli. Polymorphonuclear cells furnish the first line of defense. Phagocytic monocytes enter the field to complete the process. Failure of these cells to fulfill their respective duties ultimately results in an restricted growth of the organisms, then septicemia and death.

The Follow Up in Certain Communicable Diseases. Henry E. Stafford, M.D., Oakland, Calif

Many communicable diseases considered to be of little consequence by the average parent may establish foci of infection, reduce the efficiency of the child through fatigue and faulty posture, and lead to psychologic maladjustments. Such sequelae can often be prevented by the physician personally contacting all children two to four weeks following communicable diseases and giving them complete physical examinations.

Nasal and Bronchial Allergy Albert H. Rowe, M.D. Oakland, Calif

Nasal and bronchial allergy in childhood need constant consideration by pediatricians and especially by rhinologists. The presence of eosinophiles in the nasal secretion is important evidence in favor of allergy and may arise in inhalant and in food sensitizations. Analysis of 303 cases of bronchial asthma in childhood emphasizes the importance of food allergy during the first two years of life and the increasing importance of inhalant sensitization with advancing age. Recurrent bronchitis without evidences of asthma is frequently due to allergy. Seasonal hay fever due to pollen allergy as well as perennial hay fever due to food and inhalant sensitizations, may produce symptoms suggestive of recurrent colds or coughs, sinusitis or pharyngitis. Many of these children have concomitant cutaneous or gastrointestinal symptoms due to allergy and may have less frequent manifestations of protein sensitization such as low grade fever, cyclic vomiting and the beginning manifestations of allergic migraine. Diagnosis of inhalant allergy depends on history and scratch and intradermal testing although the occurrence of the negative skin reaction in approximately 30 per cent of such patients must be recognized. Food sensitization is often accompanied by the negative skin reaction and trial diets such as the elimination diets of the writer are of marked importance in the determination of the causative foods. The futility of surgery in the control of nasal allergy is emphasized.

Observations on Postural Treatment of Upper Respiratory Infection. Sidney N. Parkinson, M.D. Oakland, Calif

To be printed in full in the Journal.

Pediatric Dental Teamwork. Three Cases. Charles A. Sweet, D.D.S., Oakland, Calif

Three cases were reported showing the necessity of medicodental teamwork if dental caries is to be controlled in the child. One case showed the beneficial effects from an adequate intake of vitamin C the second showed the necessity of the administration of vitamin D and the third illustrated the effect of thyroid deficiency. In conclusion it was shown that there are many dietary and physical inadequacies that play most important parts in the control of dental caries. A plea was made for a more frequent formation of a medicodental team for oftentimes the mechanical correction of dental defects is insufficient.

PEDIATRIC SERVICE IN GENERAL HOSPITALS

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES OF THE AMERICAN ACADEMY OF PEDIATRICS

IN THE following series of reports we shall attempt to present at least a partial picture of pediatric care and facilities for that care in the pediatric departments of general hospitals throughout the United States. Questionnaires were sent only to hospitals having at least twenty four beds exclusively for children. Bassinets were counted in the pediatric service when the service was under the direction of a pediatrician.

The first report concerns the hospitals in Region I of the Academy of Pediatrics. This region includes the following states: Connecticut, Delaware, Maine, Maryland, Massachusetts, New Jersey, New York, Pennsylvania, Rhode Island, and the District of Columbia. This particular area is, of course, the most thickly populated in the entire country.

Total Beds—The total number of beds and bassinets by states is given in Table I.

TABLE I

STATE	NUMBER HOSPITALS	BEDS	BASSINETS	HOSPITAL WITH LARGEST NO BEDS	HOSPITAL WITH SMALLEST NO BEDS	HOSPITAL WITH LARGEST NO BASINETS	HOSPITAL WITH SMALLEST NO BASINETS
Conn	10	437	422	86	27	100	7
Del	1	35	5	0	0	0	0
Maine	4*	56	42	32	24	28	14
Maryland	2	92	56	59	33	35	21
Mass	16†	719	665	188	26	218	8
N. J.	11	474	397	90	26	98	3
Pa.	36	1,492	2,522	193	24	65	0
R. I.	3	237	94	147	42	43	21
N. Y.	50‡	3,133	1,403	326	25	127	0
D. C.	2	160	145	100	60	100	45

*Two reported.

†Fifteen reported.

‡One did not report.

In the entire region there are 135 hospitals which have a pediatric service of twenty four or more beds and bassinets. Four of these did not reply to this part of the questionnaire.

Among all the hospitals we find a total of 6,835 beds for children and 5,749 bassinets. The largest service has 326 beds for children, the smallest, twenty four. The largest number of bassinets in any one hospital is 218, the smallest, seven. New York State has fifty* hospitals maintaining at least twenty four beds exclusively for children. Pennsylvania has thirty six. No other state has more than sixteen, and Delaware reports only one.

Residents—Among the 131 hospitals considered in this report, thirty three employ resident pediatricians. Over half of this number are employed in New York State alone. Twenty nine residents are employed exclusively in the pediatric department, and in most instances they are paid a salary which varies from \$25 to \$175 per month.

*One hospital did not reply to this part of the questionnaire.

Internes.—The question on internships was designed to reveal the number of instances in which internes served exclusively in the children's department or merely went there for part of a rotating general internship. Several replies were indefinite in this distinction. In as far as we could determine, thirty hospitals employ internes on a service confined exclusively to pediatrics. Fifteen such services are in New York. Ninety-four hospitals report that the internes come to the pediatric department as part of the service of a general internship. Three hospitals apparently employ neither residents nor internes. The length of time spent on the service varies from one to six months. In most instances the service is for three months.

Attending Staff.—The total number of attending pediatricians for the 131 hospitals is 540. The length of time for these respective services varies from one to twelve months. The majority of the services are for six to twelve months. There are a few services as short as one two or three months.

Newborn Service.—Sixty-seven hospitals maintain newborn services under the care of the pediatric department. No hospital in Delaware, Maine or Maryland reports that they have such a service. New York has 26. Pennsylvania 17. No other state has more than 9.

Nursing.—One hundred sixty-one registered nurses are employed as heads of the pediatric departments, among these hospitals. Very few employ more than one head nurse, and there are a few which have none for that department alone. One hundred and twenty-one of these head nurses have had special pediatric training. In many instances however, the special training has consisted of only a three-month course or even less. Pupils nurses serve in the pediatric department in practically all of the hospitals. The usual length of the service is from three to four months.

As near as can be determined the average ratio of nurses to children and infants is 1.4. In a few instances it ran as high as 1.9 or 12.

Social Service.—Fifty-six hospitals maintain a special social service for children. Among these forty-two are in New York and Pennsylvania.

Diet Kitchen.—One hundred twenty-five hospitals maintain special diet kitchens for infants, sixty-five for children.

Schooling and Recreation.—Schooling for convalescents is provided in forty-six hospitals, and ninety-three provide recreation facilities.

Dispensary.—One hundred thirteen hospitals maintain a special department for children in the dispensary. In many instances this department is open only two or three times weekly. Average attendance in a few of these dispensaries is as low as four or five patients each session while many have forty or more. Average attendance is somewhere between twenty and thirty children. Replies to the question concerning clinic attendance did not permit us to compile very accurate figures. The pediatric staff serves in both hospital and dispensary in 104 hospitals. The resident sees service there in twenty-four instances, the interns in eighty-five.

Table II shows the number of children and newborn cared for by these hospitals in 1933, together with number of deaths, autopsies and percentage of autopsies, and deaths among the newborn and children.

DISCUSSION

In reading the above report, one must bear in mind that 12,584 does not represent the total number of beds and bassinets available for children in the hospitals of Region I. There are many other hospitals in which children are admitted regularly as patients but in which the number of beds and bassinets is less than twenty-four. In the latter hospitals there is probably no regular pediatric service

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GOOD PRACTICE IN MODERN EDUCATION

THE PEDIATRICIAN AND THE PEDAGOGUE

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THERE are so many problems which the modern pediatrician and the modern pedagogue share in common that I welcome most earnestly this opportunity to discuss with you some of them in the hope that we may come to a more complete understanding, not only of each other's practice but particularly of each other's aims and ideals.

In listening to the discussions at the meeting of the Academy this morning and this afternoon, I was very much struck by the similarity in points of view which the more modern physician and the more modern teacher hold in common. Both the teacher and the doctor are doing their best to search out the fundamental *causes* of the child's disorders and treat them rather than the *symptoms*, which for so many years apparently have been the center of attention in both professions. In this respect the doctors at present are far ahead of the teachers, but in all good modern schools you will find earnest attempts to recognize the difference between a symptom and a cause of disorder and to regard most unsocial or unusual behavior and even slowness of learning as a symptom of something rather than an evil in itself.

I am very much struck by the frequent reiteration, not only in the discussion this afternoon but also in several of the pamphlets written by members of your Academy, of the statement that in treating the child's physical disorders it was necessary always to bear in mind that he was a unit and that such an integrated whole could not be handled piecemeal. This, too, is good practice in modern education, but not always remembered by those who profess it. Just as in medicine, in education it is not possible to handle the child in pieces, to try to build his character at one time, his physical attributes at another, and to pay attention to

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his mental qualities at a third time. He is learning and growing all of the time and in almost every direction, in fact, just as in medicine, that child who grows in a most well-rounded manner in all directions seems to be the most satisfactory personality in the end.

A third point which we share in common is the fact that the primary and secondary school teachers at least are dealing with the growing organism, just as the pediatricians are, in contrast to many other of the specialists. When you are dealing with a growing organism, you have a very different problem from that which you face in dealing with one which has reached maturity. We make the mistake in schools (just as many general practitioners used to) of forgetting that a growing organism is not necessarily merely a smaller or less mature specimen of the finished product. It has an entity and personality all its own, and it behaves in a characteristic fashion in each of the several phases through which it passes, one of the most unfortunate fallacies which can be held by those who come in contact with the individual is that adult rules and patterns of behavior should be expected from or imposed upon individuals in the growing stage. Each child has his own type of behavior and checks and balances, which if allowed to grow normally usually will take care of his needs. However, the teacher must understand them just as the physician must understand them in his work.

This brings me to a fourth point which we share in common, that is the importance of the home, the family, and particularly the mother in the life of the growing child. I have heard frequently during this meeting the familiar phrase which one hears all too often among school-teachers when they are trying to diagnose and prescribe for a given case, namely "the real difficulty with this case is not so much the child himself as his mother" or "I know exactly what would cure him, but you could not get the mother to carry through such a program." This problem I believe is one in which we can prove to be of great use to each other. It frequently has been my good fortune to have an intelligent pediatrician interpret to the mother the attitude of the school regarding a certain child's behavior and the remedy suggested by the school therefor, it also has been my good fortune several times to have been able to help the parent understand the attitude and methods of the pediatrician in whose hands her child had been placed. I feel that without a doubt at least 50 per cent of the problems of a good school is the education of the parents of its children, and I suspect very strongly that this holds equally true in the case of the pediatrician.

If then we share these tasks in common and if (as I firmly believe) the school's difficulties are greatly lessened by the presence of one or two good pediatricians in the community, so too I feel sure that the work of the pediatrician is greatly benefited by the presence of a good school among his clientèle. Therefore, is it not plausible for the pediatrician to bring about the presence of such schools in his community? It has

been my experience that a good pediatrician is a man of tremendous influence among the families of his patients, and if he has a firm grasp of the possibilities which education possesses for helping the growth of the children in his community, he can bear no small amount of weight in determining the type of schools which the community will demand. Therefore, it is my purpose this evening to try to place before you a few criteria which I consider important in judging the worth of a good school. If the pediatrician can indoctrinate his community with such standards of judgment regarding matters of education, I feel confident that he will be doing a great service to the country.

In setting up such criteria, I am at once struck by the fact that again we have many things in common, for in general it is very safe to say that what is a good principle in pediatrics is also a good principle in education. For example, I have just read again Dr C Anderson Aldrich's pamphlet, "The Feeding of Children." This pamphlet is a perfect exposition of good practice in a modern school. At the outset of the article Dr Aldrich admits that "no force in the world can make a child eat who doesn't want to do so." Substitute the word "learn" for "eat" and you have a highly important underlying principle of modern education, however, one seldom admitted by teachers and even less seldom by parents. Dr Aldrich then goes on to explain the error so firmly held by so many who attempt this impossible task by stating that the crux of the matter is that what you are trying to do is not so much to get a certain amount of food into the child, but to develop an attitude in him whereby he will eat normally and naturally of his own free will. By forcing the child and coercing him by violent means you may so establish an obstinate attitude that he will become a feeding problem for the rest of his life. Dr Brennemann once told me that when he started to practice pediatrics not 10 per cent of his cases were feeding problems but that today the figure is much closer to 80 per cent. He accounts for this by the fact that parents have come to know a little bit about calories and vitamins and that standard weight charts are much more common in the homes than they used to be. As you know calories are easily measured and since the publication of Dr Holt's excellent book for the benefit of mothers, mothers have taken from his work those parts which they can understand more readily and check up on easily and now make a tremendous effort to get the required number of calories into the child. When the child is left to himself—as Dr Clara Davis' work at the Children's Memorial Hospital in Chicago proved—he experiments with various foods freely but finally arrives at a balance which proves to be about the best possible for him. There are occasional meat or starch jags, but these are followed by a brief fast and then a return to the normal diet. This is an exact parallel of what has happened in education. Parents have taken information and facts (as measured by percentages in the school, which certainly are far less

scientific and accurate as methods of measurement than the usual method employed for calories) to be the most important part of a child's education and then have endeavored to see to it that their children consumed or had stuffed into them a certain number of facts per day. These being most easily measured and the percentages, or grades, being most easily understood at home, it is not strange that great overemphasis should be placed upon them, with the same results with which you are familiar in pediatrics.

Therefore, one test of the worth of a modern school is to see whether it places the major part of the emphasis on attitudes—particularly attitudes toward learning and life. If we could persuade the parent to leave the child alone, simply seeing that the environment offered ample opportunities for normal growth, nine times out of ten the child would be cured just as he is in the feeding problems.

Moreover, the better modern schools are concerning themselves with fundamental relationships between facts rather than with the facts themselves. The facts are a means to an end and not an end in themselves. The attitude of the child toward his work, the methods he uses to do something, seem to the modern teacher to be far more important than the subject matter in which he is studying. But here, of course, we have to contend with the parents. It is so easy for them to overemphasize the importance of information to their children that they do not feel that a child is growing unless he has acquired a new set of facts to add to his store of "learned lumber" each day—never realizing that although the lumber be piled in exceedingly neat piles in the child's head, for the most part it never will be used to build anything.

In this connection it is interesting to note that some of the better psychiatrists today seem to find plenty of evidence to substantiate a belief that the same perverse attitudes which are set up in a child by a forceful feeding regime imposed upon him by his parents at an early age persist into his later high school behavior. I had an interesting experience just the other day in consulting a well-known Chicago psychiatrist regarding one of my high school girls, who at the age of sixteen seemed totally incapable of accepting information either from teachers or books in spite of an extraordinarily high intelligence quotient. When I laid her symptoms before the doctor and gave him the history of the case as far as I had it, he said to me at once, "That child was a feeding problem when she was an infant."

"How can you tell that?" I said.

"They always are," he replied.

I checked up the matter and found a history of one of the most obstinate feeding difficulties that I ever have encountered. Since that time I have found six or seven other cases of persistent resistance to adult instructions or help which also developed from an attitude created in infancy by forcing the child to accept food without setting up a satisfactory attitude toward feeding.

In my school I have found that the same type of treatment which was laid down by the pediatricians for helping cure difficult feeding cases is of benefit to the high school behavior problem of this type. If we can get the attitude of the parents changed from one of a feeling of personal affront because the child won't do as he is told to one of cooperative interest in trying to solve a difficult problem, I believe that both the teacher and the doctor will be assisted greatly.

Another aspect of the problem, and one which strikes me as a highly important matter when one is attempting to judge the worth of a school, is that of the application of the fundamental laws of learning to the curriculum and to the child's behavior. We have learned a great deal in the last twenty five years about the science of education and of child psychology, much which we have learned has become confused in people's minds and has been used badly. Much has had to be discarded after being tested thoroughly. Moreover, there is a very considerable disagreement among experts on most of these matters even now. Nevertheless, one or two principles are accepted by all intelligent members of the profession. No one will deny that without practice a person learns nothing. It does not follow that a person always learns what he practices, but it is perfectly obvious that unless he is given an opportunity to practice he will learn nothing at all. A second principle of learning which I believe to be axiomatic is that a child or an adult tends to repeat and therefore to practice those acts which bring him satisfaction and by the same token tends to discontinue and therefore not to practice those acts which bring him dissatisfaction.

These two fundamental principles would seem to be singularly simple to apply, but strangely enough this is not the case. We do not realize very often that although we are giving a child practice in a certain thing he may at the same time be practicing something else, and although we try to set up satisfaction or dissatisfaction in connection with a given act, very frequently the child in his mind connects the satisfaction or dissatisfaction with something quite different from that which we intended. A good school invariably will ask itself two questions in any learning situation: "What is the child *really* practicing at this time?" and "With what is he connecting his satisfaction or dissatisfaction?"

In addition to that a third question always is in the mind of a good teacher in a good school: namely, "What is the motive force which is driving this child in pursuing a given practice or an act?" The principle back of that is also quite obvious: namely that motives very frequently determine the value of an act. Two people may do the same thing and yet one of them working for a selfish motive will be doing a reprehensible thing and the other doing exactly the same thing from an altruistic motive, will be doing a highly commendable piece of work. Therefore, it behooves a school to see to it that its children have an opportunity to practice working for high motives rather than for low motives.

If, then, we set up rewards and punishment which are unnatural, the child will begin to work for fear of the punishment or hope of the reward, both of which are low motives. If we artificially create situations which give a child a chance to work for high motives (such as unselfishness and cooperation), we are helping him to practice and therefore to establish the habit which we would like to see in the citizens of the country today. If we artificially set up situations by establishing prizes, which necessarily turn the child away from the motive of working for the sake of the work or because it is of help to his fellows and to mankind in general, and we give him practice in getting satisfaction out of working for a low motive, it then is not surprising if after a while the habit becomes so established that it is not possible for him to act for any other reason except a selfish one or to believe that anyone else can be appealed to on any other ground.

Therefore, a good school gives its pupils every opportunity to practice receiving satisfaction from those acts of life which tend to be useful to the community as a whole—namely, the gratification and contentment that comes to one from being of use to his fellows, the ability to think things through for oneself and arrive at a sensible conclusion, and the gratification one has in knowing that one has contributed to the fund of knowledge of the world, or the comforting feeling that comes to a child when he has found himself able to work his way through his own problem to a satisfactory solution without help.

Unless a school allows a child to make his own mistakes and helps him to interpret those mistakes intelligently, he cannot grow. He merely becomes more dependent upon the adult and less able to cope with the problems of life which lie ahead of him. In this present chaotic state of civilization no adult is able to foretell what type of problem the child will face when he has been graduated from a college even four years hence. Therefore, it is not possible for us to lay down with certainty a curriculum of informational facts and skills which he will find of use upon graduation. We must turn to training him in attitudes toward work, methods of learning, and satisfactions which come from a sense of security and self-confidence and self-respect, together with a faith that in general there is order in this universe, and a law back of nearly everything, which, if we are intelligent enough to discover, we can use for ourselves and our fellows.

It is interesting to note that in the graduate schools and the professional schools you find a very decided turn toward this type of education—just as years ago the kindergarten and primary schools faced the fact squarely and developed a similar attitude. It is in the secondary schools and colleges where the poorest teaching is done today. Therefore, I hope that the pediatricians will concern themselves with the child throughout his growth through the high school years, for it is at that place that so much help is needed. I believe that no one can better give

this than the physicians with whom the child has been familiar since his infancy. In most of the graduate schools courses are being reduced in number, information as such has become more and more unimportant. Such schools as the Yale Medical School, the Dartmouth Business School, and many of the important engineering schools throughout the country constantly are coming back to the center and heart of subjects which they are teaching, leaving the minutiae of information in their subjects to come when the student begins to specialize in his chosen field of work but emphasizing more and more the value of knowing relationships between fundamental principles and ideas.

Dean Doherty, of the Yale School of Engineering, once told me that when he was a member of the staff of the General Electric Company in Schenectady, N. Y. he was in the habit of taking his problems to Dr. Steinmetz, whose laboratory was not far from his own, and that he became struck with the fact that Dr. Steinmetz helped him to solve his most baffling problems by means of the application of the most simple and elemental principles. One day Dean Doherty says he stopped in the snow between his laboratory and that of the "old man" as they called him, for it came over him that in all the times he had appealed to Dr. Steinmetz for help never once had Dr. Steinmetz told him any new fact which Dean Doherty did not already know. Yet he always had solved the problem. Therefore, it was not new knowledge which the great man could bring to him which made the difference, but new relationships between the old and fundamental principles of his field which he himself had not been able to see. It is with this in mind that the Yale Engineering School has reduced the number of its courses to two principal ones. I have seen an examination administered by that school last year, which consisted of one problem giving two simple principles (such as Boyle's law of the expansion of gases and Newton's law of motion) as the basis on which the entire problem was to be solved and then allowing the students to begin with those two and work out their applications to the case in hand.

I find that the better medical schools, too, are doing the same type of thing. The final examinations are not so much written as they are practical—to see not so much whether the student has a vast fund of information as to see if he can use the information which he has. There certainly is a strong tendency to avoid overspecialization in all professional fields, and particularly in medicine.

The same sort of thing is going on in the schools. A short time ago we tended to divide everything up into subject matter compartments with each subject carefully isolated within its own compartment and each department knowing very little about the others—usually with a supreme contempt for all but its own. This is rapidly changing in the good modern schools. The students are studying problems and not subjects in the case system developed at the Harvard Law School, the

type of method which is being used everywhere, the student learns about many phases at once. The Institute of Human Relations at Yale is another attempt to move in this direction, but you will notice that these instances all come from professional schools and not from high schools or undergraduate colleges.

The reason for this is, I am confident, that the professional school has had its product tested in the field almost immediately after leaving the school. Hence, failures come back on the school almost at once, whereas the secondary schools and colleges have not been in a position to be tested as ruthlessly and quickly by the old law of survival of the fittest among its students. The time is now at hand when the lack of such a test can no longer excuse an institution for not doing efficient work. Dr. William Palmer, the President of the College of Physicians and Surgeons in New York, told me only last year that one of the greatest difficulties that exists is to find young men who, although having been graduated from a reputable college with excellent records, were able to work by themselves on a problem which had not been analyzed for them. If given an examination which was largely a test of practical ability rather than of information and skill, they complained bitterly that it was not fair. He felt that this was because of the conditioning that they had received in the colleges from which they had been graduated.

Nearly all of the great college presidents have agreed that the real test of a student's fitness to enter college is not so much the information which is retained in his memory as the ability to continue his systematic intellectual growth by himself without a set task and without a taskmaster. Yet these very same colleges have made practically no attempts to measure the extent to which a given student possesses such an essential qualification as this. They do not seem to realize the difference in the attitude of a school toward its pupils from that of a college and professional school toward its students. In grammar school and high school the good schools are doing their best to discover and to develop in every one of their students the most of the possibilities that lie within him. It behooves the schools to bring out of the boy or girl all that it can of these qualities which may prove to be of worth later in his life. At the colleges and professional schools they look at this in a different way, there they are examining the young students to determine whether they have the necessary qualifications which are required in such large quantities for their particular field of endeavor. Somewhere in the freshman and sophomore years of college these two attitudes must find the common meeting point and a transition brought about which is not too abrupt and yet which will be complete. This, I am glad to report, is very rapidly being done, for the colleges now admit (in the more enlightened centers) that the school is not principally a place where a student *prepares* for college but that it is primarily a place

where a child is allowed to *live* and to *grow* and that his life in school is an important and integral part of his whole life and may not be slighted with impunity

It is during this very interesting phase of the latter part of the child's school life that I feel that the pediatrician can be of great service. It is when the child comes out of the formative period into the middle adolescent period (beginning at about the twelfth year) that he begins to discover his own personality. Here, because of the enormous increase in his physical and nervous faculties, the tremendous sensitiveness to light, sound and touch increases about tenfold and he becomes a particularly difficult individual to understand. He is no more like the animal which he has been up to this time than the grub is like the chrysalis, nor is he like the butterfly into which he will develop later if he is allowed to grow properly. Although in the human animal nature does not protect him against the buffets of this hard world as well as in the case of the insect with its cocoon, he is going through prodigious changes in his mental and moral make up in which he needs understanding and sympathy more than anything else. He certainly should not be expected to behave and conform to the adult pattern for which he is not yet ready. The tragedy of this situation is that the very people who are nearest and dearest to him are the ones who frequently hurt him the most.

It is at this time I have found from my experience with several hundred young adolescents, that they are seeking a friend and confidant who can help them interpret the hundreds of new and confusing sensations and impressions which come flooding in upon them every day. It is here that he needs the greatest understanding and help. It is here also, that the parents and the home need assistance in understanding their child and his peculiar actions. No one is more fitted to step into the breach than the pediatrician, who usually possesses the confidence of the family to an abounding degree and who certainly should be able to handle tactfully and sympathetically the child in question. The adjustment to authority, the adjustment to the opposite sex, the adjustment to the realities of the world around him, both social and financial, are all of exceeding difficulty and great importance to him. Particularly today when so many of the old landmarks and guideposts are gone, the advice and counsel of one who knows their past and present but also who is not a blood relation is most eagerly sought and deeply appreciated. Sometimes the child can find such a confidant in a teacher in school, if so it is well, but I feel sure that a great many more will find it in the doctor who knows the entire family situation so well and also has the great advantage over the teacher and parent of not having to seem to judge or discipline.

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Here again I feel that both the school and the doctor can be of inestimable use to each other. No school can possibly handle a child at

any one of his difficult stages, but particularly the one just mentioned, unless it knows fairly thoroughly the conditions at home, information about which the physician is in a position to give. On the other hand, I have seen many serious mistakes made by pediatricians who tried to prescribe for their patients without consulting with the school in any way, when a few moments' conversation with the teacher would have given the doctor information which easily could have prevented the mistake. The teacher's attitude and the doctor's attitude must be alike primarily, and in all good schools they are. Again I find in Dr Aldrich's pamphlet an excellent example of the attitude to which I refer, for he says that the doctor in working with the child should regard himself more as a gardener who is trying to provide the right conditions for the growth of his plants after studying them carefully to find out the differences between them than as the sculptor who is trying with hammer and chisel to shape a block of marble to his own design. Walter Lippmann once put it in an article in *New Republic*, " 'As the twig is bent so is the tree inclined' may be profoundly true, but it does not tend to make straight trees." Both the physician and the teacher are hoping to bring about trees without bends or curves in them whatsoever, normally straight and upright trees which will be a satisfaction to themselves and a pride to all who have had to do with them.

I feel sure that, if the schools and the doctors would attempt to understand each other more fully, they would find over and over again common points at which they can become of great assistance to each other. Therefore, at the risk of seeming presumptuous, I should like to urge upon the American Academy that they bear in mind at least two objectives in regard to the problem of the schools: first, that they do their best to know and to understand thoroughly the local schools in their community and that they try to judge them from the criteria which I have attempted to outline rather than from the usual points of view of fact gathering and examination marks, second, that they throw their tremendous influence (which cannot be underestimated, for a good pediatrician is literally idolized by his patients in a large percentage of the cases) toward the building and creating of good schools where the principles underlying the school are the same as those in good pediatrics. Dr Brennemann in his paper read before the Boston section of this society several years ago, in a quotation from Ralph Waldo Emerson, seemed to me to give the crux of the entire matter when he said, "Respect the child, be not too much his parent, trespass not upon his solitude." I feel that this expresses admirably the spirit of a good modern school, and that, since the influence of the pediatrician in any given community is as great as it is, I am confident that if they will throw the weight of this influence in the direction of creating schools with that spirit they could bring about a new generation of good citizens of which this country is so sorely in need during these trying times.

NEW POSSIBILITIES OF A PROGNOSTIC DIAGNOSIS IN TUBERCULOSIS OF CHILDREN

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TUBERCULOSIS is an allergic disease. Thus a deeper knowledge of tuberculosis is to be sought in the analysis of allergy.

Three points have been frequently overlooked in the conception of allergy: first of all allergy is a dynamic conception—it has its development and its course. Second, allergy should by no means signify only the change of *reactivity* under the influence of the allergene. It means also a change of *susceptibility* of the organism toward the stimulating or damaging influence of the allergene.

This last statement although of capital importance for our approach to the problem of allergy is unfortunately very difficult to understand. A very simple instance may help us to comprehend the difference between these two groups of factors, which determine allergy and which we have called 'reactivity' and 'susceptibility'.

If one individual is offended by another the result will equally depend on two groups of factors. (1) The offense will be resented differently by different individuals according to their increased or deteriorated amount of susceptibility toward the offense itself. That is one and the same offense will hurt one individual more deeply than another. (2) The reaction that the offended will undertake toward his assailant will depend not only on the degree of the feeling of being hurt, but also on the temperament and strength of the offended, and these two factors will determine his reactivity.

Thus allergy as determined by two changing groups of factors can be represented as a curve in a system of coordinates with reactivity as the abscissa and susceptibility as the ordinate. Each point of this curve would be determined by two parameters *R* and *S* and represent the actual state of allergy.

Third, in all allergic processes a rôle is played by the general biologic law frequently proved experimentally, that the reaction of the living organism, provoked by any stimulating agent, induces a change of susceptibility toward the stimulus. This change is biphasic: the reaction first increases the susceptibility toward the stimulus, in the further course of the reaction however, the susceptibility becomes less and less pronounced and finally, if the reactive process has been allowed to run to its end, the susceptibility will be reduced to naught and the living, reacting substance becomes indifferent to the stimulus.

From the Pediatric Department of The John Casimir University.
Lecture delivered on March 19 1934 at the Lister Institute of Preventive Medicine, London.

develop clinically noticeable symptoms of the disease and heal frequently without the knowledge of the patient

2 The course of allergy however can take an entirely opposite trend. Such course is characterized by an increased and accelerated growth of susceptibility as shown by curve *II*. This curve runs along the ordinate of susceptibility and expresses reduction of reactivity as susceptibility increases. It tends to meet the 0-point of the abscissa. Here we have an absolute lack of reactivity which we call "anergy". The susceptibility is at that point infinite while the reactivity is naught. The ultimate consequence of this course is obviously death. The curve represents those cases of overwhelming infection, which have no time to develop a sufficient amount of reactivity and are from the very beginning heading for ultimate catastrophe.

3 Between these two extreme poles of possibilities oscillates the course of the chronic clinical tuberculosis. Periods of preponderance of reactivity change with periods of preponderating susceptibility and the final result of the disease depends on the final turn of the curve *III* toward the abscissa or toward the ordinate.

This scheme is purely topologic. In spite of that it can be made very useful in theoretical handling of many problems of tuberculosis and gives a rational basis for a classification of tuberculous manifestations.

METHODS OF DETERMINING FACTORS R AND S (REACTIVITY AND SUSCEPTIBILITY)

It is obvious that the practical value and importance of my topologic scheme of tuberculosis would be definitely proved if it were possible to determine the factors R and S in each case of infection and at every stage of its development. The knowledge of these two parameters would enable us first to locate each case of tuberculosis in the RS plane of our system at any stage of its development (the *actual state of allergy*) and then to trace and follow up the course of allergy during the period of observation (the *road of allergy*). It is not necessary to emphasize the prognostic importance of such a possibility.

The task of the present experimental investigations, which I undertook in collaboration with my pupil, A. Chwalibogowski, was to find such a method. We thought that a possible estimation of the relationship between the two parameters R and S might be obtained from the study of the relationship between the size and the intensity of intradermal tuberculin reactions and the concentration of tuberculin used to provoke them.

Our experimental method was to inject a different concentration of tuberculin into symmetrical areas of skin of the back of each individual tested and to measure the reactions at the period of their acme in their two largest diameters. The arithmetic mean of these two measurements was considered as the largest average diameter char-

acteristic for the size of the reaction. We had then only to compare our measurements with the concentrations of the tuberculin used to investigate their possible interrelationship.

By this method we were able to detect three different types of relationship between size of intradermal tuberculin reactions and concentration of tuberculin.

1 In the first group of our children with a positive tuberculin test we could observe a marked proportionality between the size of the intradermal tuberculin reactions and the concentration of the tuberculin used. The instance in Table I is typical for this group of children.

TABLE I
No 55 Name, S— May 5, 1933

CONCENTRATION OF TUBERCULIN C	AVERAGE DIAMETER OF THE INTRADERMAL REACTIONS IN MM D	PRODUCT D (-log C)
10 ⁻⁴	18.5	74.0 (= 4 × 18.5)
10 ⁻⁵	14.0	70.0
10 ⁻⁶	12.0	72.0
10 ⁻⁷	10.5	73.5
10 ⁻⁸	9.5	76.0

Table I shows the very interesting phenomenon typical for this group of children, that the diameters of the reactions decrease with falling concentrations of tuberculin in proportion to the negative logarithm of the tuberculin concentration. Consequently, the product of the diameter by the corresponding negative logarithm of the tuberculin concentration is, in each individual of this group, constant. We may at once emphasize that this law proves to be correct only as regards medium intensity of intracutaneous tuberculin reactions and that very strong as well as very weak reactions are to be avoided.

Considering this precise proportionality between the allergic effect and the dose of the allergene as being possible only in cases in which both parameters of allergy, *R* and *S*, remain in mutual equilibrium, we call this category of allergic behavior "homodynamic allergy."

In other groups of tuberculin-positive children the above proportionality is disturbed. Supposing that this is due to an equally disturbed relationship between *R* and *S*, we call such cases "heterodynamic allergy."

Among these heterodynamic cases we can fairly distinguish between two further types.

2 In some children the diameters of the reactions do not decrease with falling concentrations of tuberculin in the expected degree. The reactions continue large. Consequently the product *D*(-log *C*) is no longer constant, but increases with falling concentrations of tuberculin. The instance cited in Table II shows this occurrence very clearly.

TABLE II
No. 75 Name, P— April 29, 1933

CONCENTRATION OF TUBERCULIN G.	AVERAGE DIAMETER OF THE INTRADERMAL REACTIONS IN MM. D	PRODUCT D (-log C)
10 ⁻²	28.0	78.0 (= 3 × 26)
10 ⁻⁴	23.0	88.0
10 ⁻⁵	20.0	100.0
10 ⁻⁶	19.0	114.0
10 ⁻⁷	17.5	122.5

We consider such cases as being due to a preponderance of susceptibility ($S > R$) and call them "heterodynamic pleoaesthetic"

3 The third group of children behaves under identical experimental conditions in an exactly reverse way, the diameters drop more quickly than might be expected with change of the tuberculin concentration. The product $D(-\log C)$ consequently falls with falling concentrations (see Table III)

TABLE III
No. 2. Name, H— Nov 23, 1933.

CONCENTRATION OF TUBERCULIN G.	AVERAGE DIAMETER OF THE INTRADERMAL REACTIONS IN MM. D.	PRODUCT D (-log C)
10 ⁻²	20.0	60.0
10 ⁻⁴	13.5	54.0
10 ⁻⁵	8.5	42.5
10 ⁻⁶	6.0	36.0

We consider this kind of heterodynamic allergy as being due to a preponderance of reactivity ($R > S$) and we call such cases *heterodynamic pleoergic*

The study of the relationship between the concentration of tuberculin and the size of the intradermal reactions makes possible a differentiation of the tuberculin allergy of the child into the following groups

- 1 Homodynamic allergy ($R = S$)
- 2 Heterodynamic allergy ($R > S$)
 - a. Pleoaesthetic ($S > R$)
 - b. Pleoergic ($R > S$)

The above differentiation of the tuberculin allergy in children has been obtained by establishing the behavior of the product $D(-\log C)$ which in cases of homodynamic allergy remains constant, falls in pleoergic, and rises in pleoaesthetic allergy, with falling concentrations of tuberculin

The further question was whether it might not be possible to obtain a notion of the actual dimensions of R and S from these experimentally

established data of the actual allergic behavior of each case. This part of our work has been carried out with the help of the distinguished mathematician, Professor Hugo Steinhaus, of the University of Lwow.

The actual state of allergy of a case, as demonstrated above, can be represented by the relationship of the diameters of the intradermal tuberculin reactions to the negative logarithm of the concentration of tuberculin. It can thus be expressed by a curve in a plane xy , where x means the negative decimal logarithm of the tuberculin concentration and y the diameter of the reaction in millimeters. By study of these experimentally obtained curves, we have been able to establish the very important biologic fact that all these curves, independently of the category of allergy, can be considered as generalized hyperbolas and expressed by the formula $y^a x = \beta$, where x means the negative decimal logarithm of the tuberculin concentration, y the diameter in mm and α and β are two characteristic parameters. The main feature of such curves is that they appear as straight lines in a plane with logarithmically divided axes. Each such line represents the actual state of allergy of a case and it can be determined by two parameters, which can easily be established both graphically and by calculation. As in cases of simple hyperbolas (e.g., in cases of homodynamic allergy) these two parameters are equal, it was obvious that we can identify them with our theoretical parameters of the actual state of allergy, R and S .

R and S can thus be easily determined from our experimental data if not graphically, with help of the logarithmic paper of Schleicher and Schuell, No. 375½, which is the easiest way, then by means of two observations (x , y , and x_1 , y_1) and the following formulas

$$R = \frac{\log x_1 \log y_1 - \log x_2 \log y_2}{\log x_1 - \log x_2}$$

$$S = \frac{\log y_1 \log x_1 - \log y_2 \log x_2}{\log y_1 - \log y_2}$$

Nevertheless, this method of establishing R and S might prove too complicated for clinical practice and consequently we worked out very simple charts which permit us to find the exact figures for R and S according to the different values of D at given tuberculin concentrations.

RELATIONSHIP OF TUBERCULIN ALLERGY TO CLINICAL BEHAVIOR

The capital question, whether the above differentiation of tuberculin allergy in children and the estimation of the actual stage of allergy by the determination of R and S have any connection with the clinical behavior, had to be solved on a large series of carefully observed clinical cases, this required a further simplification of our method. It was impossible to perform from four to six intradermal injections in each of our, now over 150, cases to establish their individual and actual state of allergy. We decided, therefore, to employ for this purpose only two injections and to choose such concentrations of tuberculin which, according to our experience, are best adapted for average testing, viz., 10^{-4} and 10^{-6} . Only in cases of exceptionally high or exceptionally low sensitivity to tuberculin (judged from a previously executed von Pirquet test) was it necessary to employ more diluted or concentrated tuberculin solutions, e.g., 10^{-5} and 10^{-7} or 10^{-3} and 10^{-5} .

We thus obtained for our estimation of the actual state of allergy in each case and at the given date, two diameters, D_1 and D_2 , corresponding to two concentrations of tuberculin, C_1 and C_2 , and could, therefore, establish the category of allergy of the given case first by means of comparing the products $P_1 = D_1(-\log C_1)$ and $P_2 = D_2(-\log C_2)$. If P_1 was equal or nearly equal P_2 , we considered our case as homodynamic, if P_1 was less than P_2 , as pleoaesthetic, and if P_1 was greater than P_2 , as pleoergic. At the same time we could, with the help of the same data, establish the actual R and S and thus locate our individual as a point in the plane RS , viz., our scheme of allergy.

Besides estimating the actual state of allergy in our cases, we tried to follow them up dynamically. In the majority of our cases we were able to repeat the determination of R and S several times during a longer period of observation. It was thus possible not only to locate each of our cases as a point in the plane RS , but also to follow up its course in time. This course we called the "road to allergy" and consider it as the most important individual feature of the biologic behavior of the organism during the tuberculous infection.

RESULTS

The results of our investigations of over 150 cases with over 300 estimations of the actual state of allergy are the following:

To avoid any influence of suggestion we divided our material into four clinically distinct groups. In Group I we summed up all tuberculin positive cases in which we could not detect any specific symptoms during a longer period of observation (*tuberculous infection without symptoms*).

To Group II belong all the suspected cases without definite symptoms or cases which recently have shown some signs of active tuberculosis, but were actually free from them (*tuberculous infection in labile equilibrium*).

Group III embraced all manifest cases of tuberculosis with a marked tendency to amelioration and recovery.

Group IV included cases with clinically bad prognosis.

This clinical differentiation of our cases proved to be almost absolutely congruent with our findings of their state of allergy.

Group I proved to belong almost without exception to the pleoergic category of allergy and to hold this position with remarkable tenacity even toward ergotropic nonspecific influences.

Group II belonged almost entirely to the homodynamic category and was particularly susceptible to all specific and nonspecific influences, as proof of its lability.

Groups III and IV were found to belong to the pleoaesthetic category. The difference between them was only of a dynamic character,

they could not be differentiated by means of a single establishment of their actual state of allergy, but their road of allergy is different. While cases of Group III are wandering from the pleoaesthetic zone in the *RS* plane toward the zones of homodynamic and pleoergic behavior, the cases of Group IV take the inverse direction. They are rushing up into still higher regions of pleoaesthesia.

The few exceptions to these rules proved by means of further observation either the superiority of the biologic method over the clinical differentiation or special conditions of allergy, which cannot be detected by our present method.

To the latter kind of exceptions belong in the first place the anergic states of allergy. The final cases of anergy, as for instance, cases of milary tuberculosis or tuberculous meningitis, behave apparently as pleoergic cases. This is theoretically fully comprehensible. Still more interesting are cases of isolated tertiary tuberculosis. Our present method of valuation of *R* and *S* cannot be applied to adults. Adults with tertiary symptoms behave like pleoergic children. This is due to the fact that the skin of adults is less sensible to tuberculin, thanks to the change in the topography of allergy in the tertiary stage of tuberculosis. This curious behavior of adults is actually the subject of extensive investigations, and we hope to elucidate this problem in the near future. For the present we are not in a position to consider tuberculosis in adults.⁴

CONCLUSIONS

1 The behavior of tuberculin-positive children toward simultaneous intradermal injections of different concentrations of tuberculin (Koch's old tuberculin) is different, and we are able to differentiate three distinct categories of tuberculin allergy in childhood.

a Homodynamic allergy, in which the product P (= diameter of skin reaction \times -log of concentration of tuberculin) is individually constant.

b Heterodynamic allergy. Pleoaesthetic—in which P increases as the tuberculin concentration falls.

c Heterodynamic allergy. Pleoergic, in which P falls as the tuberculin concentration falls.

2 The relationship between size of intradermal tuberculin reactions and concentration of tuberculin used is thus characteristic for each individual at the date of investigation and expresses the actual state of individual allergy. It can be represented by a curve in the plane xy where x is the negative logarithm of the tuberculin concentration and y the diameter of the reactions in millimeters.

3 Such curves of the individual state of allergy are generalized hyperbolas and can thus be logarithmically transformed into straight lines. This biologically most important fact permits us to determine

each of these lines—and thus each individual state of actual allergy by the help of two parameters, R and S (reactivity and susceptibility)

4 A description is given of the methods by which these parameters (R and S) can be determined.

5 The repeated determination of R and S during a certain period of observation in the same individual allows one to trace the individual "road of allergy," i.e., the direction taken by the dynamic development of the individual allergy in the RS plane

6 The determination of the actual state of individual allergy and of the individual course of allergy have an important value for prognosis in children. It has been proved on over 150 patients that stabilized and healing tuberculosis belongs to the pleoergic category of allergy, while active cases behave in a pleoaesthetic way. The homodynamic allergy is found in cases in which the state of infection is labile. The following up of the individual road of allergy reveals the prognostic fate of the case: active pleoaesthetic cases with tendency to amelioration move in the RS plane from the pleoaesthetic toward the homodynamic and finally to the pleoergic zone, pleoaesthetic progressing cases wander, on the contrary, to still higher pleoaesthetic regions.

7 Our method cannot be applied to final stages of anergy and it cannot as yet be used in adults.

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CONGENITAL DISLOCATION OF THE HIP IN INFANCY

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CONGENITAL dislocation of the hip is an important pediatric problem which has been neglected by the pediatricist. This lack of interest often has made necessary a severe treatment of years' duration in cases in which mild treatment of a few months would otherwise be possible. It has made physicians satisfied with a doubtful prognosis when they should expect an excellent one.

The basis for this lack of interest is the failure of diagnosis which is largely due in turn to an anatomical misconception. The term, congenital dislocation of the hip, is a misnomer. The condition present at birth is the absence of a bony acetabulum. There is no congenital dislocation when complications are not present. Dislocation takes place after a force is applied. This force is muscle pull alone in early infancy. Weight bearing increases the dislocation later. That dislocations can take place as a result of trauma, infections, or anomalies is not denied. These complications do not concern us here.

Instruction has been inadequate regarding early signs. It has concerned itself almost exclusively with the dislocation as it exists in children who have started to walk. The general conception has been that the diagnosis was impossible until weight bearing had forced the femora to obvious dislocations. This opinion still prevails despite a few orthopedists' vigorous attempts to correct it. The Freibergs, father and son, of Cincinnati, deserve much credit for their work in this direction. Albert H. Freiberg¹ pioneered in this country for early recognition of the condition. Paer² and Lorenz³ preceded him in the field, but their work was largely with older children. Since these early papers several workers have substantiated their conclusions. Few of these reports have appeared in pediatric journals.

The importance of early diagnosis is apparent when it is realized that abduction for a relatively short time is the only treatment required in early infancy. Freiberg treated his infants with abduction by means of casts. Vittorio Putti,⁴ of Bologna, simplified the method by using only splints and massage. The children thus treated were able to walk at the usual age. They had had no reductions and, with Putti's method, no casts.

Furthermore, this condition has been overlooked frequently by the pediatricists on account of its supposed rarity. It is not rare to the

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orthopedic surgeon. In my own pediatric practice I have had four cases in the past two years. This lifts it from the realm of rarity.

That the diagnosis is not difficult, the treatment mild, and the prognosis excellent is illustrated by the following group of infants. One was fourteen months old when she was first seen. She was beginning to walk. The others were diagnosed at two and one half months, two months, and three weeks of age, respectively. Of these four cases the child on whom the diagnosis was made after she started walking is still under treatment at the end of two years. She has had continuous casts, three closed reductions, and recently open reduction was performed. The others, diagnosed in early infancy, required only splinting and massage. The first of these, diagnosed at two and one half months, had a bilateral dislocation. She was clinically normal at eight months. An x-ray examination at that time showed beginning ossification of the acetabulum. Treatment was discontinued as the family fled to escape an epidemic. While the child was away from our care, she began standing. Subsequent x-ray plates showed continued improvement until a final one at the age of eighteen months disclosed normal acetabulum. The second, diagnosed at two months, had a left-sided, unilateral, delayed acetabular ossification. When she was four months old, Dr. Ralph S. Bromer, of the Children's Hospital, reported on her x-ray plates as follows: "There has been excellent development of the left acetabulum so that now it is approximately the same as the right. It seems to me that a diagnosis of potential dislocation is no longer warranted." Treatment of the third, through a misunderstanding, was delayed until she was three months of age. Now, at six months, she is still under treatment but her progress has been excellent, and a cure is anticipated by eight months. Diagnosis was substantiated and progress checked by stereoscopic x-ray examination in all cases. These patients were treated by Dr. Varnum Southworth, orthopedic surgeon, to whom I am greatly indebted for his invaluable cooperation. There has been only one child on whom the diagnosis was mistaken when the physical signs seemed to warrant an x-ray examination. Even in this case the hip was not normal. Dr. Henry K. Pancoast, of the University Hospital, reported "fullness of the periarticular soft tissue structures" on the affected side.

Frequency of Occurrence—This cannot be accurately estimated. In the past ten years the Children's Hospital of Philadelphia has admitted thirty cases. This gives no index to its frequency because it is solely a treatment of election. Mention is made of the number admitted simply as evidence that it is not unusual. Orthopedic wards are seldom without a case. All the patients in the Children's Hospital with one exception were girls. Two were sisters, identical twins. The family incidence was not studied. Most workers believe it occurs as a hereditary trait. During the same ten year period the Children's Hospital had only ten

diabetic patients Diabetes is not considered rare, and a higher percentage of its victims must necessarily reach hospitals

Etiology—The explanation for delayed ossification of the acetabulum can be only conjectured It does not seem to be a defect in development There are two reasons for believing this

First, it is rarely associated with other defects Twenty-nine of the above mentioned children were otherwise normal It may be significant that the thirtieth child was the only male of the series

Second, the acetabulum forms normally when the head of the femur is held in its proper position Wolff's law, regarding the changing of a bone's internal structure by its external stresses and strains, may explain the delay Normally there is muscle pull forcing the head of the femur into the acetabulum Without this pressure there would appear to be no incentive for ossification of the acetabulum That it is formed in cartilage we can hardly doubt, as it develops embryologically by the time the fetus is from 20 to 25 mm in length⁵ It is conceivable that the force may be changed in direction at times so that it be away from the pelvis A fulcrum between the hip and the knee in the fetus would cause such a reversal of force Uterine pressure upon the knee would then spring the hip from its socket The fulcrum might be formed by the crossing of the legs, by an arm between the abdomen and thigh, but more likely by a wide pelvic crest Additional evidence favoring this hypothesis is the fact that it occurs so predominantly in the female with the wider pelvis Joseph A Fierberg reached a somewhat similar conclusion Familial tendency can be explained by the inheritance of wide pelvises or characteristic postures in utero

Diagnosis—A correct anatomical concept is essential to an understanding of the condition With this in mind the signs become logical

At birth, as stated above, there is no bony acetabular formation This leaves the head of the femur unanchored Muscle splinting is required for stabilization It is analogous to a fracture in this respect All the muscles from the pelvis to the femur take part in the maneuver Even the hamstrings to the leg assist When the thigh is in a straight line with the body, the insertions of these muscles are below the femoral head with origins, on the pelvis, well above the insertions (Fig 1) Hence in this position they unite in an upward pull Great distortion is not likely, however, because of the medial origins of the muscles Only the small group of abductors do not arise medially to the head The bony structure is well designed to impede upward dislocation The flat ilium slopes outward as it arises This inclined plane helps to hold the femoral head in its intended place Eventual fatigue or stretch of the adductors permits gradual dislocation of the femur Such dislocation is a slow process Weight bearing greatly speeds the displacement

By reviewing the anatomic structures around the hip joint, the signs can be anticipated. In a child with this condition the adductor group will be the most affected by any sliding of the femur in a lateral direction. The pectineus, adductor brevis, and the upper fibers of the adductor magnus are immediately put on stretch by such a movement. To a lesser degree the gemelli, quadratus femoris and the obturators would resist the motion. The abductors, pulling from above, would be much less intimately affected.

Inasmuch as the adductors are also external rotators, stretch causes an outward rolling of the thigh. This will be directly proportional to the extent of lateral displacement.

Upward dislocation shortens the extensors and flexors of the thigh. The flexors are less completely contracted than the extensors because of their greater length. Allowance for the shortening of the hamstrings is made by flexion of the foreleg

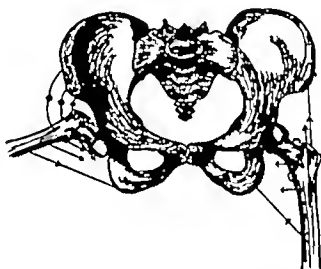


Fig. 1.—Diagrammatic representation of the muscle pull from a normal pelvis to femur. Muscles from both posterior and anterior aspects of the thigh are represented. The left side illustrates the femur in direct line with the pelvis. The right side shows the femur in abduction.

In recapitulation then, we find the femur relatively immobilized by all its muscles. There is a definite spasticity of the adductors. These are often the only signs present in early infancy. As the infant grows in strength the upward muscle pull increases the displacement and the external rotation becomes more marked. The thigh is held in almost constant flexion and the leg may resist extension.

Now let us look at a young infant with a unilateral delay of ossification of the acetabulum. The mother has noticed nothing abnormal. It lies on its back and is symptom free. Both legs are drawn up comfortably. It kicks freely with one leg while the other is held motionless. The child appears so well it is difficult to believe that only one leg is being used.

On extending both legs flat to the table one may meet with resistance on the affected side. When the legs are thus extended a somewhat

higher inguinal fold is noticed on this side producing a more acutely angulated crease (Fig 2) One must be sure that the legs are straight, as distortion is easy The gluteal fold, also, is a little higher This may produce an asymmetry of the lower spinal region which can be easily mistaken for a scoliosis This is more satisfactorily demonstrated by setting the child up In this position it will be seen that the buttocks are not equal The creases in the backs of the knees are similarly asymmetrical At the ankles the same is true Conceivably, in bilateral cases this asymmetry might not exist Practically, the two sides are not apt

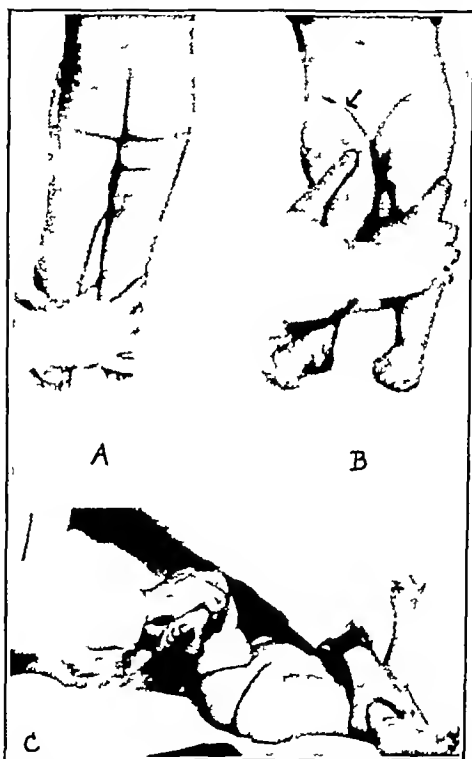


Fig 2—A. Posterior view of an infant with delayed ossification of the acetabulum on the right side. Dislocation is beginning. The asymmetry of the gluteal and knee folds is shown. Note the fold on the mesial aspect of the right thigh. This may or may not be present. See text.

B. Anterior view showing the angulation of the right inguinal fold. External rotation is present.

C. Demonstration of the limitation of abduction on the right side.

to be entirely identical in degree. Other folds are usually unimportant. For instance, there may be markedly asymmetrical creases on the medial aspects of the thighs (Fig 2). There may be none on one side or a discrepancy in number. Although a difference occurs at times in this condition, it occurs in a high percentage of normal infants as well. It seems to have little significance but is always worthy of investigation as to cause.

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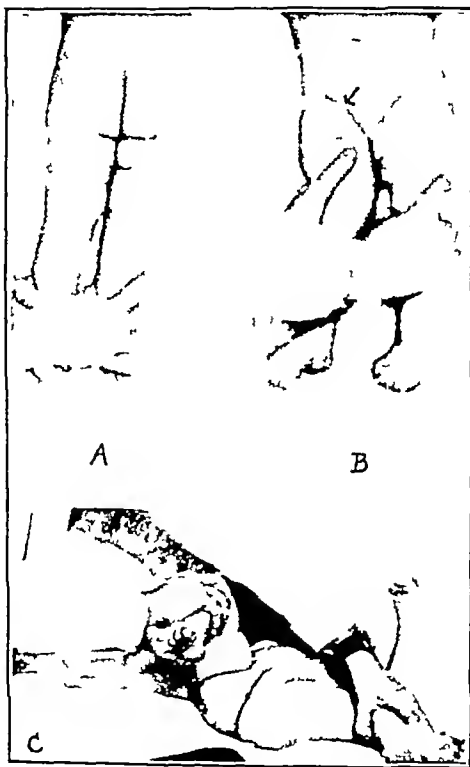


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When the knee is raised to right angles with the body, abduction in this position should be normally 75 to 90 degrees from the perpendicular. On the affected side it will be 45 degrees or less.

When any or all of these findings are present, an x ray examination is warranted. Incidentally x ray plates of delayed acetabular ossification are not frequently taken. On this account the roentgenologist is likely, with all respect to him, to be as inexperienced as the pediatrician in this condition. The plate shows, as we expected, no bony acetabular formation and little or no displacement of the head of the femur. The ilium is not angulated preparatory to the formation of a future acetabulum as it is normally, but is flat or even concave on the surface facing the femoral head. The epiphyseal center of the head is sometimes rather larger on the affected side. Its outline is irregularly ovoid as against the even circle of the normal center. Only in very early infancy is this true. As the epiphyses develop the normal side grows much faster, while ossification is slow on the affected side. Bony acetabular formation even at birth is normally evident to x ray examination.

The signs usually expected are not encountered in these early cases. There is no obvious widening of the perineum, no absence of the head of the femur from its proper site, and no widening of the pelvis. These signs do not develop until later.

Treatment—On this subject there are two schools of thought. One the conservative believes in early treatment. This takes advantage of the period of rapid bone formation. As there is no displacement to overcome at this age, only splinting is necessary. Details of this treatment will follow. The second or radical school, believes in allowing the child to develop physically to the point of more solid bone formation before therapy is begun. When this age is reached traction is applied to overcome the dislocation caused by walking and long-continued muscle pull. Closed or open reduction and often both follow it. For this group early diagnosis is nonessential.

The anatomic explanation for the success of the conservative treatment is as follows. When the thigh is held in a straight line with the body there is an upward pull from all the pelvis attached muscles. This is not the case when the thigh is in abduction. The muscles then have a medial pull (Fig 1). The origins of the muscles on stretch in this position are horizontal to or below their insertions in the thigh. Those whose origins are higher than their insertions are relaxed. The abductors are passively contracted beyond use but, if they pull at all they will pull medially. The force of the pull is medial and downward. When this direction of force is applied the head is guided into its intended place by the small muscles surrounding it, the obturators and the gemelli.

Pnatti took advantage of these anatomical facts when he began splinting the thighs in abduction. His apparatus is of two kinds. One con-

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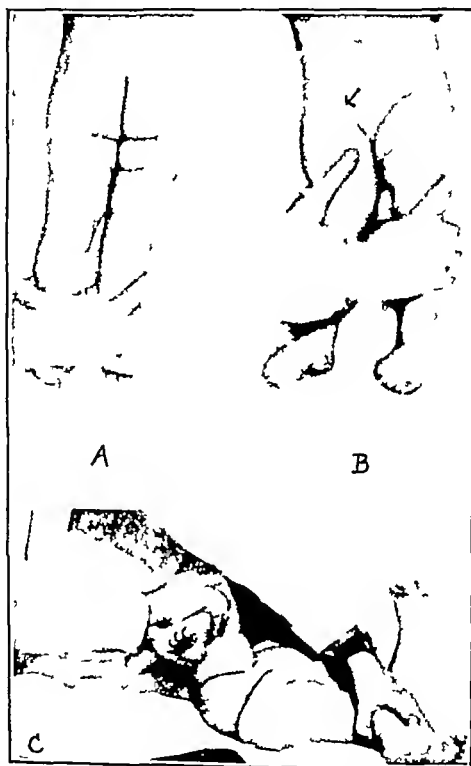


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When any or all of these findings are present, an x ray examination is warranted. Incidentally x ray plates of delayed acetabular ossification are not frequently taken. On this account the roentgenologist is likely with all respect to him to be as inexperienced as the pediatricist in this condition. The plate shows as we expected no bony acetabular formation and little or no displacement of the head of the femur. The ilium is not angulated preparatory to the formation of a future acetabulum as it is normally but is flat or even concave on the surface facing the femoral head. The epiphyseal center of the head is sometimes rather larger on the affected side. Its outline is irregularly ovoid as against the even circle of the normal center. Only in very early infancy is this true. As the epiphyses develop, the normal side grows much faster while ossification is slow on the affected side. Bony acetabular formation even at birth, is normally evident to x ray examination.

The signs usually expected are not encountered in these early cases. There is no obvious widening of the perinæum, no absence of the head of the femur from its proper site, and no widening of the pelvis. These signs do not develop until later.

Treatment—On this subject there are two schools of thought. One the conservative, believes in early treatment. This takes advantage of the period of rapid bone formation. As there is no displacement to overcome at this age only splinting is necessary. Details of this treatment will follow. The second or radical school believes in allowing the child to develop physically to the point of more solid bone formation before therapy is begun. When this age is reached traction is applied to overcome the dislocation caused by walking and long-continued muscle pull. Closed or open reduction and often both, follow it. For this group early diagnosis is nonessential.

The anatomic explanation for the success of the conservative treatment is as follows. When the thigh is held in a straight line with the body there is an upward pull from all the pelvis-attached muscles. This is not the case when the thigh is in abduction. The muscles then have a medial pull (Fig 1). The origins of the muscles on stretch in this position are horizontal to or below their insertions in the thigh. Those whose origins are higher than their insertions are relaxed. The abductors are passively contracted beyond use but, if they pull at all they will pull medially. The force of the pull is medial and downward. When this direction of force is applied the head is guided into its intended place by the small muscles surrounding it, the obturators and the gemelli.

Putti took advantage of these anatomical facts when he began splinting the thighs in abduction. His apparatus is of two kinds. One con-

sists of boards strapped on the inner surfaces of the thighs and hinged together at the perineum. The amount of abduction is controlled by an umbrella staff arrangement with a setscrew. His other is a cushion, triangular in shape, with straps on two sides to be secured in a similar manner to the inner aspects of the thighs. Other orthopedists have devised apparatus equally simple in nature. C. H. Jaeger,⁸ in his method, uses pressure pads above the head of the femur to ensure its descent into the acetabulum. Joseph A. Freiberg⁷ has an ingenious method of accomplishing the same effect. He uses individual casts, one on each leg to the mid-thigh. Between the ankles is a turnbuckle to control the abduction and to form a fulcrum on which a turnbuckle between the knees pulls in adduction. M. Forriester-Brown⁸ uses metal splints on the external aspects of the thighs. These are hinged to similar strips

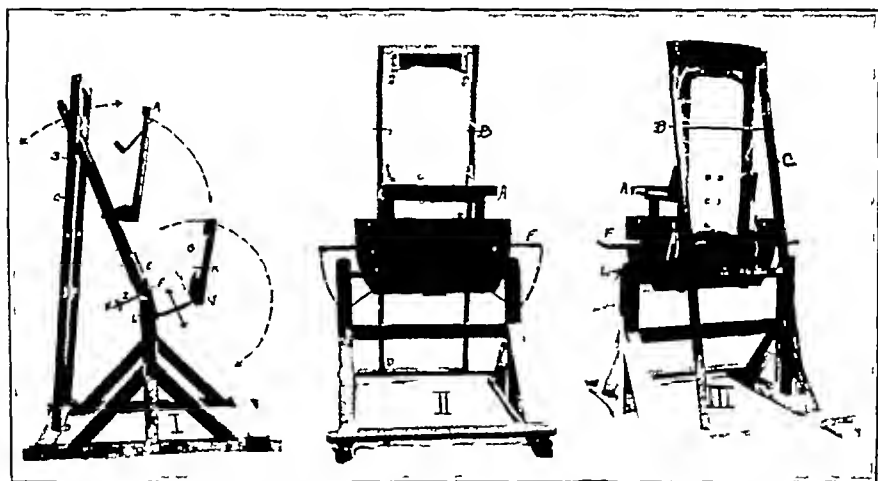


Fig 3—Chair-bed abduction apparatus

I Lateral aspect with the arcs of variations in dotted lines

A feeding tray B crossbar. This can be removed and inserted into holes seen lower on back-rest. C, back-rest. This is hinged at D. F Putti type of abduction splint. It is built in two halves hinged in the middle at E. Each side is adjustable to the desired angle where it is held by the removable peg K. G Anterior plate, hinged at the bottom. It is secured in the upright position by hook, J. This slips over the end of bolt, H. The tension spring I, permits the anterior plate to have a little forward motion. The entire apparatus can be inclined on the axis L to any angle from vertical to horizontal.

II Anterior aspect of the chair-bed in the upright position. The possible variation of angle of the abduction splint, F is shown in diagrammatic lines.

III Posterolateral aspect. Note holes through both posterior and anterior plates for the pegs which hold the adjustable splint. The posterior plate is cut away inside the back frame, to the level of the splint. This allows room for the buttocks. The canvas back is of Bradford frame dimensions.

strapped to the sides of the body. This apparatus has the advantage of simplifying excretory hygiene.

These methods of treatment require the recumbent position. This is the comfortable and logical posture for infants under six months of age. At approximately this age a normal child begins to sit up. Those with delayed ossification of their acetabuli, being normal otherwise, at-

tempt it. Frustrated by the apparatus, they become fretful and irritable. There is no contraindication to the sitting posture so long as abduction can be maintained. This position has an advantage over the recumbent posture because the weight of the child can be utilized in



Fig. 4.—Patient A. C. C. aged two and one-half months. bilateral delay of ossification of acetabuli.



Fig. 5.—Patient A. C. C., aged four months. Plate shows good position of femoral heads with abduction alone. No reduction was necessary.

forcing abduction. With this object in mind a chairlike apparatus was built. In it is incorporated an adjustable Putti abduction splint as a seat. The back is similar to a Bradford frame in shape and dimensions with canvas stretched over its uprights. Anterior and posterior to the

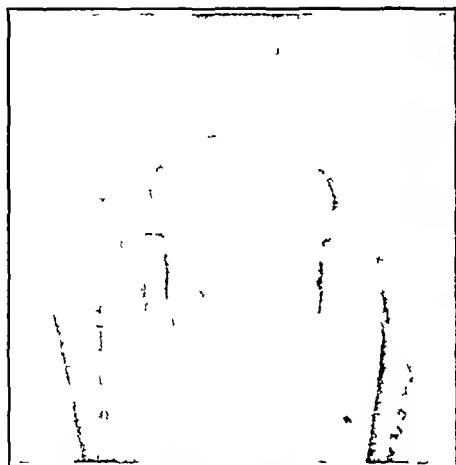


Fig 6

Fig 6—Patient A. C. C. aged eighteen months



Fig 7

Fig 7—Patient J. W. aged three weeks delay of acetabular formation on right side.



Fig 8

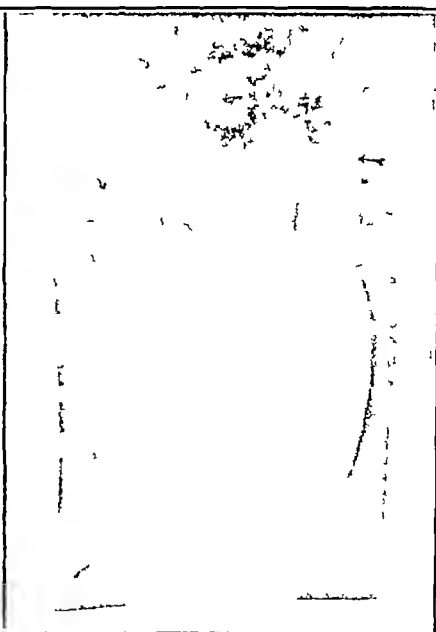


Fig 9

Fig 8—Patient A. W. aged two months. Note that the epiphyseal center of the femoral head is larger and less dense on the affected side than on the normal. Its shape is irregularly ovoid as against the even circle of the normal.

Fig 9—Patient A. W. aged four months. Note great improvement in acetabular ossification.

splint are retaining plates to keep the legs in position. The anterior is hinged at the bottom and held parallel to the posterior one by an adjustable tension spring. This permits occasional bending of the knees but the spring pressure soon tires the leg and forces it straight again. A second advantage in the hinging of the anterior plate lies in the fact that it can be swung out of the way to facilitate seating and removing the baby, thus allowing the infant to be readily lifted out for the changing of diapers. There are no straps and buckles for the mother or nurse to struggle with. For feeding and amusement purposes a tray similar to those on high chairs was added. The entire apparatus can be inclined on its base and held at any angle, thus forming a chair by day and a bed by night. The infant may sit, lounge, lie prone or supine as seems the most comfortable. This apparatus allows the child to lead a normal life while undergoing treatment.

SUMMARY

1 We believe there is no dislocation of the hip at birth except in the presence of complications. There is instead, a delay in bony acetabular formation.

2 A plea is made that pediatricists consider the early recognition of this condition as their problem.

3 The relative frequency of its occurrence is emphasized.

4 The signs on which the diagnosis should be suspected are reviewed and explained anatomically.

5 A new apparatus for abduction therapy is described.

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GREENE AND COULTER STREETS

PHYSICAL MEASUREMENT AND NUTRITIONAL STATUS

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THE weight for height tables stimulated great interest in malnutrition of school children for many years. But the assumption that these tables could be used as a valuable index of nutritional status has interfered with sound clinical procedure in the selection of undernourished children in many schools. A knowledge of the factors which influence the weight of school age children has shown that weight for height is more nearly an indication of certain kinds of skeletal build than of nutritional status.¹

The new ACH index of nutritional status² should revive interest in malnutrition of school children because of its economy in eliminating the many cases that are most likely to be well nourished,³ and therefore allowing more time to be given to school physical examinations of a small group of children containing a high proportion with poor nutrition. The American Child Health Association has recently published tables⁴ for an evaluation of three physical signs of nutritional status that the writer has used in school examinations during the past year. As this experience has indicated various applications of these measurements, several cases are presented with a discussion of their interpretation in the interest of further study and testing of the new measurements on an extensive scale.

Table I gives the status of eight children in three physical signs of nutritional status. They were referred by teachers for special examination for various causes including suspected malnutrition. In the opinion of the writer they are representative of some of the various types of poorly nourished children found in public schools in need of medical health supervision. The figures for each measurement for a particular child show the number in 1,000 of his or her peers who are lower in the given measurement than the particular child. The 1,000 peers used for comparison with each case are representative of children of the same age and sex having the same combination of height, hip, chest breadth, and chest depth dimensions.

The first two children, Ruth and James, are quite obviously undernourished children. Both are much underweight for their build. In a random 1,000 eleven-year-old girls with the same combination of height, hip, chest breadth, and chest depth dimensions, only eleven children, or 1 per cent, would be found who did not weigh more than Ruth. Among seven-year-old boys with the same four skeletal dimensions as James, only twenty would weigh less. They are both children with small mus-

culature when compared with their skeletal peers Ruth's musculature is so small that a smaller arm girth would be found not more than seven times in a random 1,000 girls eleven years old with the same skeletal

TABLE I

STATUS DISTINCTIONS OF CHILDREN IN WEIGHT ARM GIRTH, AND SUBCUTANEOUS TISSUE

COMPARED WITH THEIR PEERS IN BODY BUILD

NAME	AGE	SEX	STATUS DISTINC TIONS NUMBER IN 1 000 LOWER THAN EACH CHILD			ACTUAL HEIGHT INCHES	ACTUAL WEIGHT POUNDS	AV LB. WT FOR HEIGHT†	POUNDS WT FOR BUILD‡
			WEIGHT	ARM GIRTH	SUBCUTANEOUS TISSUE				
Ruth	11	F	11	7	60	51	53	63	55
James	7	M	20	60	200	47	48	50	49½
Georgiana	9	F	55	159	41	50½	56½	61	63½
Shirley	9	F	14	270	80	54½	68½	70	77½
George	8	M	40	212	250	50½	58½	58	64½
Edward	7	M	68	90	500	48½	47½	53	52
Rose	9	F	5½	98	120	49½	57½	55	61½
Frances	8	F	55	105	450	49½	55½	56	61½

The figures for each measurement for a particular child show the number in 1 000 of his or her peers who are lower in the given measurement than the particular child. The 1 000 peers used for comparison with each case are representative of children of the same age and sex having the same combination of height, hips, chest breadth, and chest depth dimensions.

†Compared with Baldwin Wood tables.

‡Compared with peers of the same height, hips, chest breadth, and chest depth dimensions.

dimensions, and only 60, or 6 per cent, would have as small arm girth as James among his peers. They are also low in the amount of subcutaneous tissue as measured by the thickness of the skin fold over the biceps with special subcutaneous tissue calipers*. This measurement on Ruth indicates only 60, or 6 per cent out of 1,000 girls of the same age and with the same skeletal dimensions would have a smaller amount of subcutaneous tissue, and 200 boys, or 20 per cent, would have as small an amount as James.

Both of these children are well below average for their age and sex in all four skeletal dimensions. Even with average weight, musculature, and adiposity children with such slender frames are likely to give the impression of thinness. These children are so unusually low in all three physical signs that they appear thin and frail and suggest poor nutrition to the casual observer. The clinical examination also shows very little flesh over the chest, well-defined winged scapulae, and soft flabby muscles.

The third child, Georgiana, has about average skeletal proportions and is not so obviously underdeveloped in musculature and adipose tissue

Her measurements, however, indicate she is sufficiently underweight for her skeletal dimensions and with arm girth and amount of subcutaneous tissue so unusually low that further inquiry regarding her nutritional status is advisable. Only fifty-five in a random 1,000 of her peers in skeletal dimensions would weigh as little as she, and only 159 in 1,000 would have smaller arm girth and forty-four would have a smaller amount of subcutaneous tissue. According to the Baldwin-Wood tables, average weight would be 61 pounds, while average weight for nine-year-old girls with her skeletal dimensions is $63\frac{1}{2}$ pounds. Although we have said Georgiana has about average skeletal proportions, actually she is about 1 inch below average height and slightly below in chest breadth, chest depth, and hip dimensions, which fact accounts for an average weight for build which is $2\frac{1}{2}$ pounds above the average for the tables based on height. While the difference in this case seems to be small between the average weight for the Baldwin-Wood tables and the average for four skeletal dimensions, we may explain that her biologic position as indicated by 55 in 1,000 is unusual because variations in weight of school age children is very largely influenced by the skeletal dimensions, and there is generally little variation from the average weight derived from four skeletal dimensions.

It may be seen that the fourth child, Shirley, is very low in weight for build and low in amount of subcutaneous tissue, but she has an arm girth somewhat better than the previously mentioned children. This girl has badly infected tonsils with recurrent tonsillitis and acute cervical adenitis, she failed to gain weight during our three-month period of observation. Other evidences of malnutrition in this case are limited energy and rather feeble endurance. We might expect to see a satisfactory gain with the removal of this focus of infection.

George, the fifth child, is very much underweight for his build but less underdeveloped in musculature and adipose tissue than the other children. He has a fair musculature over the chest and in no way appears emaciated. He is a rather large boy for his age being above average in height, both chest dimensions, and hips. His mother reported that he had no appetite for breakfast and asked that he have a mid-morning milk lunch in school. It seems quite possible that this boy may have had a spurt of skeletal growth which accounted for his underweight and small sized musculature and adiposity in proportion to his frame. Four months later he had gained four pounds, and his arm girth was average for his build.

Edward's weight and his musculature status is very low, and his subcutaneous tissue is average for his build. He is of about average height with about average chest breadth and a shallow chest and narrow hips. Both arms and legs appear very thin, and his muscles are very soft and flabby. This child is one of nine children. The family is entirely dependent on public relief, investigation shows a diet of excess starches

foods which may account for his adipose tissue. During six months' observation he gained only $\frac{1}{2}$ pound.

Rose is low in all three physical signs although she is $21\frac{1}{2}$ pounds above average weight for her height. She has been a preventorium patient because of hilum tubercular infection. When first examined she gave the impression of having a well developed musculature because she is short and has an unusually broad and deep chest with average width hips. This kind of frame is difficult to judge without measurement and the greater weight, musculature, and adipose tissue appropriate for her frame was not readily appreciated without the tables for comparing her measurements. Her poor development was more apparent six months later when because of poor home conditions she had not gained in weight, and she had gained 1 inch in height. Then her posture definitely indicated her poor muscle tone, and the depressed intercostal spaces emphasized a thin chest.

Frances is another child of average weight for height, but she is under weight and with undersized musculature for her stocky frame. She is average height and above average in chest breadth more than one sigma above average in chest depth and above average in hip width. Her nearly average amount of subcutaneous tissue is probably due to a diet of excess starch and sweets. She has very badly decayed teeth and lives under very poor home conditions.

These measurements compared with a random 1 000 children of the same skeletal build are not in themselves an evaluation of nutritional status but they do give reliable objective, and valid distinctions in weight, musculature, and adiposity which are significant in such an appraisal. They are indices of physical signs which should be properly evaluated in a composite of signs and symptoms. Of course deviations from an average should not be interpreted directly as desirable and undesirable signs but the average provides a convenient reference point which gives definiteness to the measurements. The use of accurate distinctions in these three physical signs releases the clinician from the difficulties of individual judgment and gives him greater freedom to apply all the subtleties of the art of medicine in judging function, growth and development and all the intricate factors involved in the nutritional process.

The appraisal of the nutritional status as a basis for health supervision requires a consideration of the whole child, his social setting and the coordination of many factors which may influence his well being. But so far as reliance is placed upon the evaluation of physical signs observable at any one time it is important that this evidence be dependable. The pediatrician evaluates muscular development and adiposity every day in his clinical appraisal of nutritional status. He generally considers the weight to determine the over all growth but he recognizes the

need for improved criteria in order that he may interpret properly the individual differences in weight. Any general conclusion about the muscular development must be built up from estimates of various muscles or groups of muscles. Such estimates, of course, are difficult to make accurately without measurements and standards. This is especially true because the size of the skeletal framework influences so much the size of the muscles and allowance cannot be made for the type of build since children do not readily fall into types of skeletal proportions but present all possible kinds of combinations of chest breadth and depth, height, and hips. This is shown by some of the cases presented above.

Malnutrition has been regarded by some as a clinical entity.⁶ Then the diagnosis presumes the recognition of a well-defined syndrome. Of course, the occasional case may be found which presents a clinical picture very similar to the textbook description of malnutrition. In most cases, however, the picture is blurred by a variation in the degree to which the signs and symptoms are clearly recognizable. Good nutrition and malnutrition are obviously the extremes of a scale. The significant signs and symptoms are variable rather than categorical distinctions. While malnutrition may be a useful term to designate extreme cases, the pediatrician who would give advice and guidance relative to nutrition cannot afford to limit his service to the typical cases of malnutrition.

Such a definite appraisal of three morphologic factors raises questions of the share of immediate and remote influences that are responsible for changes in musculature, adiposity, and over-all growth as revealed by weight. The gain or loss in weight may continue to be our most satisfactory measurement for children followed over a period of time, but the measurement of these important physical signs is, in the experience of the writer, most valuable in evaluating nutritional status of the children seen for the first time because it contributes evidence that is free from personal judgment. It seems reasonable to expect that further study of our cases with the help of these measurements may reveal that diet, excess fatigue, foci of infection, or other etiologic factors may show rather immediate manifestations in muscular development or in the limitation of subcutaneous fat. Deficiencies in function such as digestive disturbances, nervousness, hyperirritability, overactivity, restlessness, and anorexia may be findings which may possibly be associated with certain kinds of development. The secondary anemia, the soft and flabby muscles, the poor circulation, and limited energy or definitely feeble endurance are the kind of advanced manifestations of malnutrition which we should like to prevent. One of the handicaps we have labored under in the prevention of malnutrition has been our limitations in the evaluation of physical signs of the more or less well child. Precisely measured physical signs should help to overcome this handicap and offer further prospect of recognition of premonitory signs of malnutrition.

SUMMARY

Numerical distinctions in weight musculature, and subcutaneous tissue are reported for eight children with proper allowance made for differences in four skeletal dimensions

These distinctions are presented as objective and valid physical signs of nutritional status The interpretation of these physical signs is discussed Deviations from an average in indices of physical signs is interpreted as a valuable aid in the appraisal of nutritional status at any one time A proper evaluation of these three physical signs in a composite of all signs and symptoms is proposed as a possible means of a better understanding of the nutritional process and of determining premonitory signs of malnutrition

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270 ROSE STREET

BRAIN TUMORS IN CHILDHOOD

REVIEW OF THIRTY-EIGHT CASES

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FROM the standpoint of the pediatrician the diagnosis of intracranial tumors has a practical clinical application. It is not necessary to have a highly specialized neurologic training in order to arrive at a tentative diagnosis of brain tumor. Too frequently, however, in dealing with children, the possibility of such a lesion is not given sufficient regard. In reviewing our charts we found evidence that not infrequently brain tumor was a late, rather than an early, consideration. In this presentation the authors make no effort toward fine neurologic distinctions. Emphasis will be placed on the more obvious signs and symptoms encountered in children suffering from intracranial tumors.

This report is based on a series of verified and suspected brain tumors in children who were admitted to the Children's Hospital of Los Angeles from Jan 1, 1924, to May 1, 1934. During this decade there were 11,340 admissions to the medical service. Our group comprises thirty-eight cases, giving a ratio of 0.335 per cent, or one brain tumor in every 298.6 medical admissions. None of these children had reached the thirteenth birthday.

It has been estimated by Williams¹ that brain tumors in general represent about 1.8 per cent of all tumors of the body. Brain tumors are said to be relatively less frequent in children than in adults, Cushing² giving the ratio of approximately one tumor in childhood to six in adult life. Certain types of tumors frequently seen in adults, i.e., meningiomas, acoustic neuromas, and pituitary adenomas, seldom if ever occur in children under twelve years of age. The proportion of gliomas in children is therefore increased and is approximately 75 per cent of all intracranial tumors, while in adults the percentage would range from 37 per cent to 42 per cent. Cushing raises the question whether or not many more brain tumors go unrecognized in children than in adults. The majority of these are various types of gliomas with an occasional tuberculoma and rarely a congenital cystic tumor. The cerebellum is the seat of predilection for gliomas in children. Cushing gives the ratio of cerebellar to cerebral tumors as 2 to 1 in children, as compared to 1 to 5 in adults.

In this study we have considered tuberculomas in the category of tumors because it is difficult to distinguish between the two types of lesions clinically. Tuberculomas are said by Bailey³ to be "four times

as frequent in children as in adults' They are, however relatively infrequent as compared to gliomas even in children (ratio 1 to 10) and rarely occur in adults When present in children tuberculomas are said to occur more frequently in the cerebellum This was also our experience, as out of three cases two were in the cerebellum and one in the right parietal lobe The tuberculomas represented 7.8 per cent of the entire series All were in Mexican children

Of this group of thirty eight tumors (Table I) eighteen have been verified as some type of glioma either by operation or autopsy three as tuberculomas, and one as a Rathke's pouch cyst and one as a cholesteatoma In fifteen not verified by tissue study, the diagnosis

TABLE I
TYPES OF TUMORS

Gliomas (verified)	18
Gliomas (probable but not verified)*	15
Tuberculomas (verified)	3
Rathke's pouch cyst (verified)	1
Cholesteatoma (verified)	1
Gummas	0
Total	38

*These fifteen cases not verified by tissue study, were in all probability gliomas of some type.

of brain tumor is considered as highly probable There was no gumma in this series and in only one instance was there a positive blood Wassermann reaction in which a verified glioma (probable medulloblastoma of the fourth ventricle) existed The cerebrospinal fluid Wassermann reaction in this case was negative This bears out the well known fact that cerebral gummas are very rare and that gliomas may develop in syphilitic patients

The cases of both verified (Table II) and unverified but probable tumors (Table III) have been grouped according to the general location of the growth Approximately two-thirds of the verified tumors 69.5 per cent and a majority of the unverified tumors, 60 per cent,

TABLE II
LOCATION OF VERIFIED TUMORS

Rathke's pouch cyst	1
Third ventricle	2
Right cerebral hemisphere	4
Left cerebral hemisphere	0
Midbrain	0
Fourth ventricle	8
Right cerebellar lobe	2
Left cerebellar lobe	1
Cerebellum (bilateral)	2
Medulla	1
Vermis	2
Unlocalized	0
Total	23

Of these 69.5 per cent were subtentorial

were subtentorial. The majority of these posterior fossa lesions were either in the fourth ventricle or in some portion of the cerebellum. The ratio of subtentorial to supratentorial tumors in the verified group was approximately 7 to 3, while in the unverified group the ratio was 3 to 2 making the proportion of cerebellar, as compared to cerebral, lesions in our series somewhat greater than the established figures.

TABLE III
CLINICAL LOCATION OF UNVERIFIED TUMORS*

Rathke's pouch cyst	1
Third ventricle	2
Right cerebral hemisphere	1
Left cerebral hemisphere	0
Midbrain	2
Fourth ventricle	2
Right cerebellar lobe	2
Left cerebellar lobe	1
Cerebellum (bilateral)	2
Medulla	0
Vermis	0
Unlocalized	2
Total	15

*Of these 60 per cent were subtentorial.

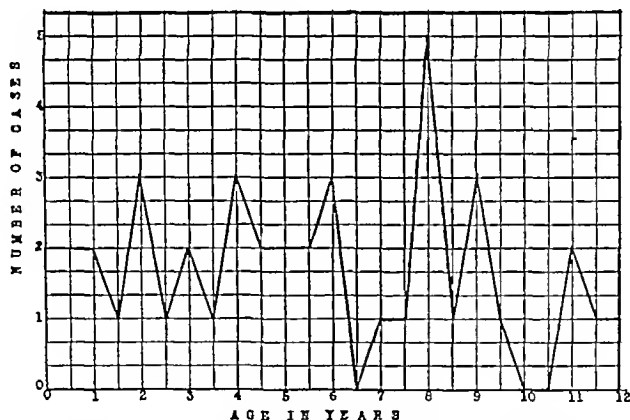


Chart 1—Graph showing the relative frequency of tumors at various ages. The greatest number occurred at eight years of age. The others showed no predilection for any particular age.

AGE OF INCIDENCE (CHART 1)

In considering the age incidence, one is immediately impressed by the fact that early age is not an argument against the possibility of the presence of a brain tumor. The youngest patient was an infant of ten months on whom a diagnosis of encephalitis had been made. The spinal fluid contained thirty-three cells and increased globulin and was under increased pressure. An intracranial tumor was not suspected, but upon autopsy multiple gliomas of the cerebellum with spontaneous hemorrhages were found. The next youngest child,

eleven months old, had a fourth ventricle tumor, probably a medullo blastoma. The discs were not choked. The spinal fluid in this instance was under increased pressure, contained no cells, and gave a negative globulin test. There was paralysis of the right third and sixth cranial nerves, accompanied by hydrocephalus and convulsions. The greatest number of tumors five in all, occurred in an eight year old child. The remaining thirty one cases showed no predilection for any age but were scattered over an age period from one to twelve years.

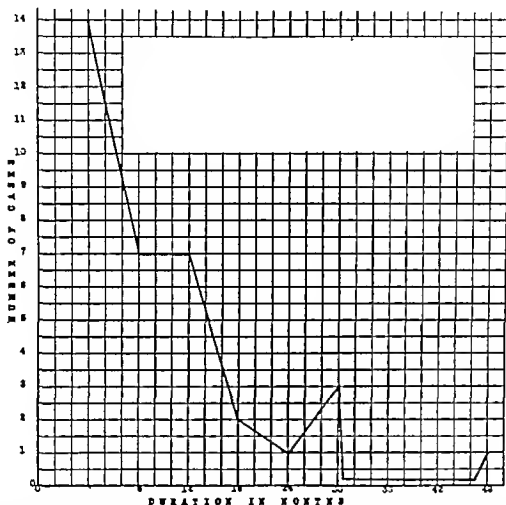


Chart 2.—Graph showing duration of symptoms in months before admission. All patients had symptoms one month or more before being seen. Three patients not included in this graph had symptoms five, eight, and five years, respectively before being seen. One of these was a cystic glioma, the other two cystic congenital tumors.

DURATION OF SYMPTOMS IN MONTHS BEFORE ADMISSION (CHART 2)

If one is confronted with a child who has been sick only a few hours or possibly days the probability of a brain tumor is remote. This is well brought out in Chart 2. Fourteen of the children had symptoms for at least from one to three months before admission. Fourteen additional cases showed symptoms from six months to a year previous to hospitalization. Two patients had symptoms for eighteen months, one, for two years, three, for two and one-half years, and one, for four years before admission. Three additional cases were not included

in this graph because their symptoms had covered a period of years rather than months, being five, eight, and five years, respectively. One of these was a cystic tumor of the vermis (probably an astrocytoma), the second was a suprasellar (Rathke's pouch) cyst, the third was a cholesteatoma in the neighborhood of the optic chiasm, invading the third ventricle. In other words, the first of these last three cases was cystic, the other two were both cystic and congenital. All of these conditions would imply slow growth and bespeak a relatively long prodromal period.

RELATIVE FREQUENCY OF PRESENTING SYMPTOMS (CHART 3)

The time element does not preclude the possibility that the physician may be confronted with an acute emergency in a child suffering from a brain tumor. The parents may give a history which on the surface

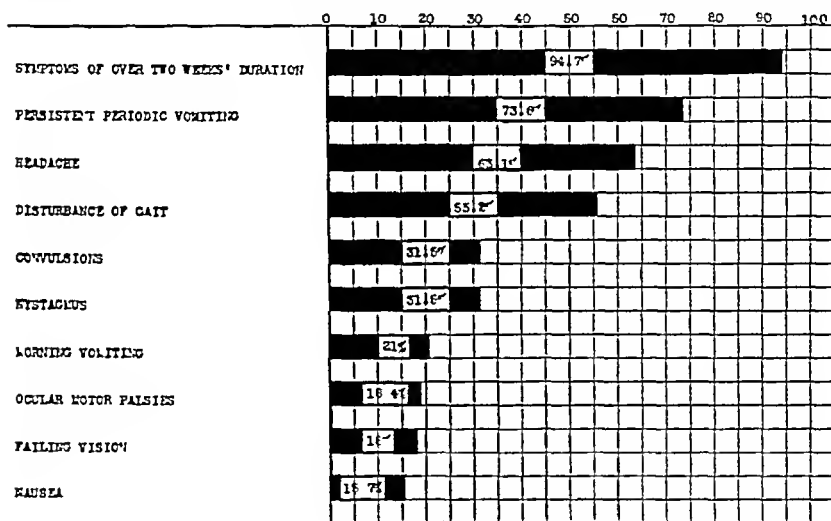


Chart 3—Graph showing relative frequency of principal presenting symptoms

would seem to point to a short illness overlooking symptoms which go back over a period of time. These symptoms may have seemed to them to be of little significance but in reality are of utmost importance. Morning vomiting may be given as an example. One is more apt to be misled in a child who has been ill from three to six months than in a child who presents an emergency. Of these cases, 94.7 per cent give a history of over two weeks' duration.

Persistent Periodic Vomiting (Chart 3)—In general it seems that vomiting which is of central origin, whether it be from a brain tumor, meningitis, or craniocerebral injury, is sudden and not preceded by any period of nausea. This has been called, sometimes erroneously, projectile vomiting. Some of the cases presenting difficulty in diagnosis were of children who were considered to have gastrointestinal

disturbances. In most instances careful studies were made of the gastrointestinal system before intracranial tumor was considered. It would seem the part of wisdom that all patients being treated for regulation of diet should have ophthalmoscopic examinations if vomiting persists over one week. This is illustrated by our series in which 73.6 per cent presented the complaint of persistent periodic vomiting while 21 per cent complained only of morning vomiting.

An attempt was made to analyze the symptom of vomiting. This was done for two reasons. In the first place vomiting while not always associated with serious consequences is a very common complaint of childhood and in the second place, it was the outstanding symptom in this group. Two types of vomiting were encountered. The first was persistent periodic vomiting which failed to be explained by the physical examination. It occurred at any time during the day but seldom, if ever awoke a child from his sleep. This is in contradistinction to vomiting due to appendicitis, intussusception and other gastrointestinal disorders in which the child may be awakened with vomiting. If the mother says the child is awakened by vomiting, it usually signifies some intestinal disorder. The second type occurred only in the morning and will be discussed later.

Anyone who observes large groups of children in hospitals must be impressed by the fact that it is a rare thing for a child, regardless of his social status or home training, to vomit without making some attempt to reach for a basin or show other instinctive methods to protect himself and his surroundings. On the other hand, the child with a brain tumor has little or no warning. One may find him with the bedclothing soiled or if vomiting is projectile in type the vomitus may be on the floor or wall. Usually the child is as surprised as the attendant who discovers him.

Headache (Chart 3)—Pediatricians generally agree that it is relatively infrequent for a child to complain voluntarily of headache. If a child complains of headache, a pediatrician should carefully inquire into the cause. At the same time one must learn to differentiate between the headaches described by nervous, interested parents and the headache that a child will mention of his own volition. All will agree that headache in a child is a serious complaint if it is frequent or persistent. The type of headache does not necessarily indicate the location of the tumor. However, it is well known that occipital or suboccipital pain is more common in posterior fossa lesions. This may be associated with stiffness of the neck or suboccipital tenderness. The fact that cerebellar tumors sooner or later will cause a block of the aqueduct of Sylvius with resultant hydrocephalus would indicate that in time the headache may become general. Pain in the forehead, temples or vertex may occur with a tumor in almost any location. Suboccipital tenderness, however, should be emphasized in view of the

fact that approximately two-thirds of the brain tumors in childhood are below the tentorium. The headache may, or may not, be associated with vomiting. In this series headache was complained of in 63.1 per cent of the cases.

If a child is old enough to answer questions, there is little difficulty in getting the history of headache. He may greet you with the words, "Don't touch my head," even before the question is asked. Younger children will put their hands to their heads or rub their heads on the pillow. When headache is pronounced, the child is usually lethargic and may become comatose.

In adults bradycardia is often associated with headache when intracranial tumors are present. This is usually not the case in children. It was not found in our series.

Disturbance of Gait (Chart 3)—Most of the disturbances of gait have been in the nature of ataxia. Stumbling and falling, especially in younger children, have been prominent. On the other hand, staggering is infrequent in children with early fourth ventricle tumors. For a considerable period of time they may be even agile on their feet, being able to climb trees, roller skate, or run like their playmates. Occasionally incoordination was first noticed when the child could not ride his bicycle or use roller skates properly. As the tumor grows and begins to impinge upon or invade the cerebellar hemispheres, gait disturbances become more evident. On the other hand, a tumor beginning in one cerebellar lobe may evidence itself by early gait disturbance. In our series 55.2 per cent complained of gait disturbance. Practically all of these patients had posterior fossa lesions of one type or another. Not all of the cerebellar patients, especially with the fourth ventricle tumors, had ataxia. Loss of balance sense and stumbling in a child is often looked upon as awkwardness by the parents, and little significance is attached to it. It is difficult, often impossible, in a child of two or three years to get valuable information from the gait. It is well known that these children have their good days and their bad days. On one day the examiner may elicit no disturbances in gait, on another the ataxia is only too evident. The mother often calls this to the physician's attention. Incoordination of the upper extremities, while less frequent than of the lower, may occur. The child may be awkward in feeding or dressing himself. He cannot perform fine movements with his hands.

If the tumor is in the vermis, there is usually incoordination of the trunkal muscles. Such a child, if pushed backward from the standing position, cannot save himself from falling by shifting his center of gravity. He falls like a top because he cannot throw his pelvis forward. Again crawling or creeping in young children may be impossible because they cannot synergize the action of their trunkal muscles with those of their extremities.

Hemiplegic gaits may be seen if the lesion is near either motor strip but these are less frequent in children than in adults

Convulsions (Chart 3)—Convulsions during childhood are, generally speaking rather frequent. They may at times be the first clinical manifestation of almost any acute infection. In general it may be said convulsions are most frequently associated with febrile states. One valuable aid in the diagnosis of convulsions due to brain tumor is that they are not associated with any marked elevation of temperature. While epilepsy is not uncommon in children, it was rather striking that not once was this diagnosis made in this series of brain tumors. The characteristics of the typical epileptic fit are well known. The type of convulsion associated with decerebrate rigidity is not infrequent in cerebellar tumors or those about the brain stem but is practically never seen in the true epileptic.

While convulsions do not constitute a very prominent symptom in this series, 31.5 per cent their presence was almost always of serious import. Convulsions were more frequent in children under two years of age than in the older ones. They were seldom of any localizing value. No instance of jacksonian epilepsy was recorded in this series. In only one instance did a child with a brain tumor survive more than three weeks after the onset of convulsions. This was the case of a five and one half year old girl presumably with a fourth ventricle tumor who died three months after admission. Children with tumors who have convulsions are perhaps less likely to have associated loss of sphincter control than epileptics.

Nystagmus (Chart 3)—Nystagmus was present in approximately half of the cases of cerebellar tumor. It was not constant often coming on relatively late. It should be emphasized that nystagmus is seldom present early in fourth ventricle or even in vermis tumors. About half of the cerebellar tumors were in the midline and consequently did not cause nystagmus. When present, however especially if associated with headache or vomiting nystagmus should be considered as very significant. Nystagmus was found in this series in the same proportion as convulsions, namely 31.5 per cent. The two however had no relationship. No attempt will be made to analyze the various forms of spontaneous nystagmus. Suffice it to say that horizontal nystagmus is by far the most frequent.

Morning Vomiting (Chart 3)—In a relatively large percentage of early fourth ventricle tumors morning vomiting may be the only presenting symptom. This may continue for weeks or months before other symptoms appear. Any child with persistent repeated morning vomiting should be looked upon with suspicion from the standpoint of a possible fourth ventricle tumor. Not infrequently these children have been considered as presenting behavior problems or of being of a neuropathic constitution. The vomiting may have been considered

as a subterfuge on the part of the child to prevent him from going to school or from being obliged to perform some other distasteful duty. It is a significant fact that morning vomiting may appear alone for a long time, the child not vomiting at any other time in the twenty-four hours.

In observing these cases we were impressed with the fact that not infrequently a child was sent into the hospital for vomiting but while in the hospital the patient did not vomit. This would seem to be misleading. In an analysis of this, it would seem that we did not bear in mind the difference in routine between the hospital and the home, the main point being that while a child is in the hospital, he is not allowed to be up and about. One is therefore led to believe that morning vomiting may be induced by sudden change of posture associated with arising in the morning. Consequently, these hospitalized children, being kept in bed, are less likely to vomit.

It has been said that a child with morning vomiting, enlargement of the head, and headache gives presumptive evidence of a fourth ventricle tumor.

Ocular Motor Palsies (Chart 3)—Strabismus of one sort or another is relatively frequent among otherwise healthy children. One can always find cross eyed children in a hospital. Not infrequently operations are performed in children's hospitals for imbalance of ocular muscles. However, there may be a significant neurologic background for these conditions. In seven of our children, 18.4 per cent of the series, bilateral internal strabismus occurred twice, unilateral ptosis and bilateral ptosis once each, and unilateral internal strabismus three times. It is well known that paralysis of the abducens nerve is a notoriously unreliable sign. It is frequently seen in internal hydrocephalus from any cause, the sixth nerve being the longest and consequently most liable to trauma.

Failing Vision (Charts 3 and 4)—A special graph has been made showing the relative frequency of choked discs as compared with the infrequent subjective complaint of failing vision (Chart 4). In only 18 per cent of the cases were visual disturbances mentioned in the history, while ophthalmoscopic examination revealed the presence of choked discs in 73.6 per cent of the series. In several instances the diagnosis of tumor was either missed, or considerably delayed, because the eyegrounds were not examined. In view of the fact that the discs are choked in 73 per cent or more of cases of brain tumor, one cannot refrain from emphasizing again the importance of this examination. Every pediatrician should be able to recognize whether or not the eyegrounds are normal. Ordinary choking of the discs is a characteristic picture and should occasion little difficulty of recognition. One should not wait, especially in children, for a history of failing vision before

examination of the fundi. A child should never be fitted for glasses without first having an ophthalmoscopic examination.

Nausea (Chart 3)—Nausea is difficult to define. It is purely a subjective symptom. It not only implies being "sick to the stomach" but a loathing for food. Patients who are nauseated will not eat. This holds true in children as in adults. When present it occurred relatively late and comprised only 15.7 per cent of the cases. It was not nearly as frequent as vomiting (73.6 per cent). The child with a brain tumor may vomit frequently but in the interim will usually take food readily. We know of no other condition in which this is true except perhaps in pyloric stenosis. In this respect only, do these two conditions resemble one another.

Spinal Fluid Findings (Chart 5)—Spinal fluid examinations were made in 70.2 per cent of the cases. It is generally considered that lum

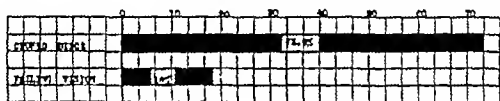


Chart 4.—Graph showing relative frequency of choked discs as contrasted to the frequent complaint of falling vision.

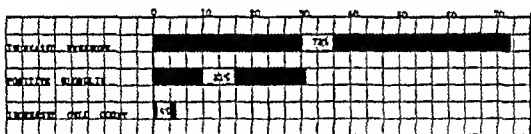


Chart 5.—Graph showing spinal fluid findings in 70.2 per cent of the cases.

bar puncture is attended with considerable risk in cases of brain tumor. This is especially so if a tumor is suspected in the posterior fossa. The danger lies in the risk of herniation of the cerebellar tonsils into the foramen magnum with consequent embarrassment of the medullary centers. In view of the fact that a large percentage of the tumors were in the cerebellar region we admit freely that a considerable hazard was entailed in carrying out these studies. Fortunately no harmful results occurred.

In spite of the fact that no ill effects followed lumbar puncture, we do not wish to leave the impression that we advocate its promiscuous use. When it is employed it should be performed carefully in the horizontal position with the use of a manometer. In this way the outflow of fluid can be kept under control and the pressure more accurately measured. The measurement of spinal fluid pressure is one of the most accurate indices of the existing degree of intracranial

pressure and in this respect is of value. Struggling, which frequently occurs in children, during lumbar puncture must be taken into account in estimating pressure readings.

Seventy-three per cent of our spinal fluid examinations showed increased pressure. The pressure, unfortunately, was not accurately measured with a manometer and depended upon the estimation of the observer. In 31 per cent the globulin was increased. This was seldom the case if the tumor chanced to be in the fourth ventricle. This was contrary to our expectations. The cell count was increased in only 4 per cent of the cases. In this hospital a cell count up to ten is considered within normal limits. In only three cases did the count rise above this, being respectively, nineteen, thirty-three, and one hundred twenty cells. In the three cases of tuberculoma, the first had no spinal fluid examination, the second contained seven cells and no increase in globulin, and the third resulted in a bloody tap and was not repeated.

Errors in Diagnosis (Table IV) —Errors in diagnosis are excusable at some stage in almost every disease. Symptoms are kaleidoscopic, they seldom follow the definite chronologic sequence as described in textbooks. The impression gained at the first examination is often changed after further study. Consequently, there is frequently a wide divergence of opinion between the admitting diagnosis and the final diagnosis in any group of cases. In the series under consideration a correct clinical diagnosis was arrived at in 70.9 per cent of the cases. With a relatively large group of unverified tumors one cannot be sure regarding the series as a whole. Table IV, "Errors in Diagnosis," has been prepared to bring out the differences between the admitting diagnosis and the final diagnosis. The principal source of error in each instance has been listed. In the eleven cases cited the constant source of error which existed was failure to examine the eyegrounds. When this was done, the physician was put on the right track. It demonstrates very clearly the fact that mistakes often happen not because of lack of general knowledge but because of incomplete examination. Three cases tentatively diagnosed as encephalitis have been cited. These all proved at autopsy to be tumors of some part of the cerebellum. The existence of encephalitis, especially soon after the influenza epidemic of 1918, was very frequent. During the latter years it has been seen with diminishing frequency. Postinfluenzal and possibly postvaccinal encephalitis are among the most common forms in children. The encephalitis form of poliomyelitis should always be borne in mind. These conditions are usually associated with a rise in temperature and often with signs of meningeal irritation. Such would not be the case in a tumor. Choking of the discs, while rare, may be present in acute encephalitis.

Dietary disturbances are very common among young children. It is, therefore, not surprising that a case of brain tumor with vomiting should be admitted under this heading. The same may be said of acidosis. Two cases have been listed as behavior problems or neuro-pathic constitution. Morning vomiting was a presenting symptom in both. They had been followed a number of months in a child's guidance clinic, where it was considered that vomiting was a subterfuge on the part of the child to prevent his going to school. They were treated for some time as behavior problems. Finally fundus examinations, made because of headaches, clarified the diagnosis. One case of

TABLE IV
ERROR IN DIAGNOSIS

ADMITTING DIAGNOSIS	FINAL DIAGNOSIS	SOURCE OF ERRORS
Encephalitis	Tumor left cerebellum	Eyegrounds not examined
Encephalitis	Tumor third ventricle	Eyegrounds not examined Misinterpretation of history
Encephalitis	Tumor right cerebral hemisphere	Eyegrounds not examined No x ray study
Diet regulation	Tumor third ventricle	Eyegrounds not examined.
Diet regulation	Glioma	Eyegrounds not examined. No x ray study No spinal fluid study
Diet regulation Acidosis	Tumor fourth ventricle	Eyegrounds not examined
Allergy		
Acidosis, Sinusitis	Tumor, midline cerebellar	Fitted for glasses without fundus examination.
Behavior problem	Tumor, cerebellum	Eyegrounds not examined
Rickets	Tumor, left cerebellum	Eyegrounds not examined. Misinterpretation of history
Swollen arm Convulsions	Tuberculoma, cerebellum	Eyegrounds not examined. No x ray study Spinal fluid not properly examined
Neuropathic constitution	Tumor fourth ventricle	Eyegrounds not examined No x ray study

rickets which resulted in death from a tumor of the left cerebellum was incorrectly diagnosed because of lack of eyeground examination and misinterpretation of the history. In reviewing the history in the light of postmortem findings, we find one should have been at least suspicious of a brain tumor. The diagnosis of rickets was correct but had nothing to do with the cause of death. Autopsy showed an unsuspected tumor.

One child was admitted with swelling of the arm and draining cervical adenitis. Both were tuberculous. While under treatment he had a convulsion which was disregarded, and the child was discharged. Upon readmission tuberculous meningitis was suspected and a spinal fluid examination was made. A bloody tap resulted and the nasal tests could not be made. It was not repeated as should

have been done. No roentgen ray study of the skull was carried out. The fundi were never examined. Autopsy revealed a tuberculoma of the cerebellum.

ROENTGENOLOGIC STUDIES

Stereoscopic roentgenologic examinations of the skull are highly important in any case of suspected brain tumor. It is realized that in young children this is difficult, and sometimes impossible, to accomplish. However, the effort should be made. In the majority of cases the findings will consist of increased convolutional pressure atrophy and separation of the sutures. In this series these changes were present in 52.7 per cent of the cases. Convolutional markings alone are perhaps of no great significance, for it has been shown by Eaton⁴ that they occur frequently in normal children under the age of twelve. He thinks general nutritional changes may be a factor in their production. When found in conjunction with separation of the sutures, convolutional atrophy has definite significance. This is especially true if accompanied by measurable enlargement of the head. The tendency for the infant to decompress himself by widening of the sutures and fontanelles must be kept in mind. When this occurs, signs of increased pressure as manifested by headaches and choking of the discs may be delayed. In certain cases of pituitary disorder alteration in the sella turcica may be present. This would constitute a very small proportion.

Since the use of air as a diagnostic measure was introduced by Dandy,⁵ ventriculography has been employed with increasing frequency. It is a valuable asset. We have seldom used air when a cerebellar lesion is suspected, first, because internal hydrocephalus, which accompanies these tumors, can be easily recognized in children from ordinary roentgenographic studies and accurately confirmed by Macewen's sign (cracked-pot note elicited by percussion of the calvarium), second, there is considerable risk following ventriculography in obstructive hydrocephalus, a high temperature reaction often resulting unless the air is immediately removed, and third, ventricular estimation can be easily done by simply tapping the ventricles preparatory to a cerebellar exploration. In supratentorial lesions ventriculography has greater value. Encephalography, the introduction of air by spinal route, should probably seldom, if ever, be used in cases of suspected brain tumor accompanied by clinical signs of increased intracranial pressure.

Cysts in the region of the sella turcica may be shown by roentgenologic examination. A case in point will be discussed.

J. R., male, aged nine years, was admitted on June 20, 1928, and dismissed July 15, 1928. He was seen by a number of men on the staff, including one of the writers. Several men felt that he had a brain tumor, probably in the cerebellar region. Vestibular studies pointed to a lesion of the right cerebellopontile angle. A visual field examination, even roughly made, was not recorded. Roent

genologic studies were conducted, flat plates being used. These consisted of roentgenographs of the head long bones, chest and sinuses. No adventitious shadows were seen in the head. This child was taken to the Mayo Clinic where on Aug 6 1928 we learned that bitemporal hemianopsia was demonstrated and a calcification above the sella turcica was revealed by x ray examination. He was considered to have a cyst near the optic chiasm. At operation it proved to be a calcareocholesteatoma containing a large amount of fluid rich in cholesterol crystals. He was discharged from that institution as improved. It is well pointed out by Balloy⁷ that certain tumors about the pituitary region give symptoms simulating cerebellar disease. However our error in diagnosis lay in the fact that visual field examinations were not made and sufficiently careful roentgenologic studies were not conducted. Had we found the bitemporal hemianopsia and the suprasellar shadow both of which were undoubtedly present the case would have been clarified.

A second case (26-294 Feb 15, 1926 26 758 May 31, 1926 and 28 958, May 14 1928) is called to attention. This case that of a little girl, nine and a half years old who had fairly typical signs of hypopituitary disease presenting a picture of Fröhlich's syndrome first came under observation in February, 1926. Roentgen ray studies of her head showed marked convolutional impressions some enlargement of the sella turcica, and narrowing of the posterior clinoid processes. A supposed pituitary adenoma was diagnosed, and the child was operated upon. Fragments of what appeared to be a somewhat enlarged pituitary gland were removed. Microscopic sections showed these to be made up of squamous epithelium. The significance of this was not apparent at the time. There was gratifying improvement which lasted for a period of years. Finally her symptoms of headache and visual disturbance recurred and she was reoperated upon Apr 19 1933 when a very large suprasellar or Rathke's pouch, cyst was encountered. During the intervening eight years she had developed suprasellar shadows which were plainly seen in subsequent plates and which in themselves were enough to make a diagnosis. She died on Dec. 23 1933, almost eight years after first being seen. This is the longest survival period of any case. During our period of observation we were permitted to see the laying down of calcium in this craniopharyngeal pouch cyst as evidenced by repeated roentgen ray examinations.

NEUROOTOLOGIC STUDIES (TABLE V)

Neurootologic studies have been of great value. Examination of the eighth cranial nerve in some respects is analogous to the examination of the second and frequently assumes priority over the optic nerve in disclosing the location of an intracranial lesion. Whether or not true choking of the eighth nerve exists in brain tumor cases is a question. However abnormalities in the function of both auditory and vestibular components of this nerve may be of distinct value. This is particularly true of the intracranial vestibular pathways. The examination of these pathways in children is more difficult than in adults, owing to the children's inability to cooperate. However, certain rather definite conclusions may be drawn in the majority of cases. Differential diagnosis between a subtentorial or a supratentorial lesion can be made with considerable certainty. This in itself is of great value, especially if the lesion be subtentorial, as the usual cerebellar exploration gives adequate exposure to handle any lesion which may be encountered in the posterior fossa.

In thirteen cases neurotologic studies were carried out (Table V) In nine instances in which the diagnosis of a posterior fossa lesion was suggested by means of studies of the vestibular mechanism, eight were correct In one of these a lesion was predicated in the right cerebellopontile angle This proved to be a cholesteatoma in the region of the chiasm invading the third ventricle In another instance the vestibular reactions were considered as normal, but a craniopharyngeal pouch cyst was found at operation In still another instance,

TABLE V

ANALYSIS OF NEUROTOLOGIC IMPRESSIONS COMPARED WITH TUMOR LOCATION

NEUROTOLOGIC IMPRESSIONS	LOCATION OF TUMOR	TYPE OF TUMOR
Postfossa lesion—probably brain stem	Fourth ventricle	Spongioblastoma multiforme
Right cerebellar lesion—pressure on brain stem	Right cerebellar tumor extending into cerebellopontine angle	Ghoma (type not given)
Suggest lesion—fourth ventricle	Fourth ventricle tumor	Medulloblastoma (?)
Suggest cerebellar involvement	Left cerebellar lobe	Medulloblastoma
Suggest posterior fossa lesion—not definite	Fourth ventricle—extending to left cerebellar lobe	Medulloblastoma
Suggest posterior fossa lesion—probably brain stem involved (A frontal lobe tumor will sometimes simulate this)	Fourth ventricle tumor	Medulloblastoma
Suggest left cerebellar lesion	Cystic tumor from vermis involving left cerebellar lobe	Medulloblastoma
Probably posterior fossa lesion	Vermis—cerebellum	Medulloblastoma
Cerebellopontine angle (left), or cerebellar tumor (left) extending into the angle	Postchiasmal and third ventricle	Cholesteatoma
Picture suggests posterior fossa lesion, probably left cerebellar	Medulla	Spongioblastoma multiforme
Posterior fossa intact	Suprasellar	Rathke's pouch cyst
Intracranial tumor—coma prevents localization	Right temporal lobe	Spongioblastoma multiforme (?)
Midline supratentorial lesion	Right occipital lobe	Spongioblastoma multiforme

in an already comatose child, the tests could not be completed, and no conclusions could be drawn At autopsy a fourth ventricle tumor was found Following one neurotologic study a middle supratentorial lesion was predicated At autopsy a spongioblastoma multiforme of the right occipital lobe was found Perimetric fields and ventriculography would have made the location of the lesion more precise

PATHOLOGY (TABLE VI)

End-results in verified brain tumor cases are seldom tabulated or published Van Wageningen⁸ recently has summarized the end-results of 149 cases of verified brain tumors from Cushing's clinic eight years

after operation The expectancy of the children with gliomas taken as a whole, was 38.8 mo The survival period of children with midline cerebellar medulloblastomas was 14.5 mo The patients with cere

TABLE VI
TYPE AND LOCATION OF PROVED LESIONS WITH SURVIVAL PERIODS

SEX	AGE	OPERATION	TYPE OF LESION	LOCATION OF LESION	SURVIVAL PERIOD
Female	3 yr 6 mo.	None	Medulloblastoma	Left cerebellar lobe	4 yr 6 mo
Female	2 yr	Partial removal	Medulloblastoma	Left cerebellar lobe	5 mo
Female	10 mo	None	Multiple gliomas	Right and left cerebellar hemispheres	1 mo
Female	11 mo	None	Medulloblastoma	Fourth ventricle growing forward	16 days
Female	6 yr	Exposed—not removed	Medulloblastoma	Fourth ventricle	3 yr
Male	9 yr	Exposed by Adson. Partial removal	Cholesteatoma	Postclival and third ventricle	5 yr + (may be living)
Male	6 yr	Partially removed	Medulloblastoma	Vermis—cerebellum	10 mo
Male	11 yr 6 mo	Not removed	Spongiblastoma multiforme	Right occipital lobe	4 yr
Female	3 yr	Partially removed	Medulloblastoma	Fourth ventricle	1 yr (?)
Male	8 yr	None	Glioma (spongiblastoma multiforme?)	Right temporal lobe	8 mo
Male	5 yr 9 mo	Fragment removed	Spongiblastoma multiforme	Medulla	8 wk.
Male	2 yr 8 mo	Partially removed	Medulloblastoma	Left cerebellar lobe	9 mo
Female	9 yr 6 mo	Partial removal on two occasions	Rathke's pouch cyst	Suprasellar	8 yr 6 mo
Male	9 yr	Partially removed	Spongiblastoma multiforme	Fourth ventricle	6 mo
Female	2 yr	None	Cystic (colloid ?)	Third ventricle	4 mo
Male	4 yr	None	Medulloblastoma	Fourth ventricle, growing forward	13 mo
Male	7 yr	Partial removal	Medulloblastoma	Fourth ventricle	Living over 7 yr
Female	8 yr	Ventricle tap	Glioma (unclassified)	Right cerebellar lobe	4 yr
Female	2 yr	None	Tuberculoma	Multiple (1) left temporal lobe (2) right cerebellar lobe (3) left cerebellar lobe	3 mo
Male	7 yr 6 mo	Partial removal	Tuberculoma tuberculous meningitis	Right cerebellar lobe	2 yr
Female	2 yr 11 mo	None	Tuberculoma tuberculous meningitis	Right parietal lobe	10½ mo

bellar astrocytomas however did much better the average survival period being nine years.

Our group of children in whom lesions were verified showed an unusually high percentage of malignant tumors The operative results

were discouraging. Indeed, only one child of this entire group is known to be living today. The pathologic records in the earlier cases were incomplete. Twenty-one cases in which the pathology was definite have been listed. There were nine medulloblastomas, five of which originated in the fourth ventricle, one in the vermis, two in the left cerebellar lobe, and one in the right cerebellar lobe. The longest survival period for these tumors was over seven years, in a lad who has had intensive postoperative high voltage therapy. The shortest survival period of this group was sixteen days, in an eleven-month-old infant. There were two cases of spongioblastoma multiforme, one occurring in the right occipital lobe and the second, an atypical form of this tumor, invading the medulla. The first was explored, but the tumor was not removed at operation. The child lived four months. A third (probably a spongioblastoma multiforme) occurred in the right temporal lobe. These tumors were all supratentorial as compared with the subtentorial medulloblastomas mentioned above. There were two unclassified gliomas, the second of which was multiple occurring in a ten-month-old infant. No cystic tumors were encountered, and no astrocytomas were identified. There was one cystic tumor of the third ventricle in a two-year-old child. This case occurred early in the series, and the specimen has been lost. One wonders if it may not have been the relatively benign colloid type of cyst occurring in the third ventricle, which has recently been so well described by Dandy.⁹ A second unusual congenital tumor was a cholesteatoma in the region of the postchiasm and third ventricle. There was one typical Rathke's pouch cyst with a survival period of eight and one-half years from the earliest symptom. During this little girl's life the tumor was twice operated upon and partially removed. Suprasellar calcification was seen to develop during this interval. There were three tuberculomas, one partially removed from the right cerebellar lobe and a second in the right parietal lobe, which was not explored, and a third presenting multiple tuberculomas in the left temporal, right cerebral, and left cerebral lobes, respectively. All of these children died of tuberculous meningitis. The longest survival period was two years, the shortest survival period three months.

SUMMARY AND CONCLUSIONS

A résumé of thirty-eight cases of verified and highly probable intracranial tumors in children has been attempted. None of the children had reached his thirteenth birthday, and the majority of them were under ten years of age. The group as a whole was younger than is usual in preadolescents, in whom the age of puberty is approaching. More exact diagnoses should have been made and better results obtained. However, the same could probably be said in the majority of

children's hospitals in this country so far as the diagnosis and treatment of such lesions is concerned

Much more could be accomplished by greater attention to the common presenting symptoms i. e., persistent periodic vomiting headache disturbances in gait ocular motor palsies of various types, enlargement of the head, failing vision nausea, convulsions morning vomiting, and nystagmus These are of common occurrences They have been recorded in the relative frequency of their appearance

Doubtless many cases of cerebral tumor in small children are not recognized Histories should be more carefully taken One can learn much from mothers The pitfalls in diagnosis, as we have found them in reviewing our cases have been pointed out Without exception the lack of use of the ophthalmoscope has been most evident We have seen children treated as behavior problems because they vomited their breakfasts—children in whom brain tumors were later diagnosed In other children extensive gastrointestinal investigations, which could have been obviated by the use of the ophthalmoscope were carried out because of vomiting We have seen children with failing vision from brain tumors fitted to glasses without fundus examination We believe that if every pediatrician would use his ophthalmoscope diligently many cases otherwise overlooked would be correctly diagnosed Little that is new has been presented in this report We trust however that the more important symptoms have been sufficiently emphasized to aid in earlier diagnoses of brain tumor in children

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SUPPURATION OF THE MIDDLE EAR COMPLICATED BY
LABYRINTHITIS, SINUS THROMBOSIS, CEREBELLAR
ABSCESS, AND CEREBELLAR HERNIA
WITH COMPLETE RECOVERY

CASE REPORT

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SUPPURATION of the middle ear complicated by labyrinthitis and sinus thrombosis is so infrequently seen as to warrant its report. However, the addition of a disturbing complicating factor of a cerebellar abscess with a herniation of the brain through the original mastoid incision certainly increases the interest and rarity of such a development. A case such as this with complete recovery except for the brain protrusion at the site of the original operation is reported.

A short discussion of the pathway of invasion of the infection to the labyrinth and its spread to the lateral sinus and cerebellum will follow. To quote F W Watkin-Thomas,¹ "the path of invasion is usually (1) through the bone by invasion, (2) through the windows either by necrosis or loosening of the stapes or destruction of the membrana tympani secundaria of the round window (this is the more common route in the acute cases), (3) through perilymphine cells (rare), (4) erosion of superior canal by extradural abscess (rare), and (5) operative injury to external canal of dislocation of the stapes."

After the labyrinth became involved in our case, the infection spread rapidly to the sigmoid sinus. J G Druss² said, "Infection of the labyrinth may spread to the sigmoid sinus along preformed as well as along newly formed pathways. The saccus endolymphaticus and the labyrinthine veins are the most common of the preformed routes. The newly formed routes consist of fistulas from within the labyrinth through the semicircular canals or through the body of the labyrinth. The saccus endolymphaticus is a narrow pouch between the layers of the dura, which communicates with the endolymph space of the labyrinth through the ductus endolymphaticus. It is situated in the posterior surface of the petrous pyramid, midway between the medial border of the sigmoid sinus and the internal auditory meatus. An infection in the saccus may spread between the layers of the dura and produce a cerebellar abscess, it may involve adjacent bone and produce a huge extradural abscess, it may involve the pia arachnoid and cause meningitis or finally it may extend along the dura to the sinus and cause sinus thrombosis. Infection

of the labyrinth may reach the sigmoid sinus through the labyrinthine veins which empty into the inferior petrosal veins or the jugular bulb. From these structures an infection may spread laterally to the sinus."

CASE REPORT

A girl, six years old, was admitted to the hospital on June 6, 1931, complaining of pain, fever and discharging right ear following an upper respiratory infection. The family history is unimportant. The child complained of an earache thirteen days before admission. There was a spontaneous rupture of the right drum followed by a profuse purulent discharge in twenty four hours. The physical examination of the child was essentially negative except for the local ear findings. There was a profuse purulent discharge from the right ear canal with definite tenderness over the mastoid tip. There was no swelling in the postauricular region. Otoscopic examination revealed that the discharge was pulsating. There was a small perforation in the drum. A definite sagging of the posterior wall in the bony meatus was observed. Blood study at this time showed W.B.C., 19,600 polymorphonuclears 87



FIG 1.

lymphocytes, 13 per cent. The temperature was 103° F. The progress of the case can be followed more closely by a study of the continuation notes of the hospital record.

June 5 1931, P.M. A right mastoidectomy was performed in the usual manner. At operation the mastoid cells were filled with greenish pus; the body and antrum showed considerable softening. The sinus was uncovered at the knee and was normal in appearance.

June 8 1931. Three days postoperative. The child complained of marked dizziness on attempting to sit up. There was definite nystagmus to the left (first degree). Hearing was definitely involved on the right side (noise test). There were no signs of meningeal irritation or involvement. The impression at this time was serous labyrinthitis (complete final recovery without loss of hearing proved this diagnosis). Temperature still ranging between 103° and 104° F.

June 11 1931. Child was desperately sick. Temperature rose to 106° F. Blood culture positive for *Streptococcus hemolyticus* (20 colonies in 1 c.c.) Blood study at this time revealed hemoglobin, 60 per cent; red cells 3,400,000; white cells 32,700; polymorphonuclears, 81 per cent; lymphocytes 19 per cent. Ligation of right jugular was immediately performed. Sinus wall was grey and thick. Mural

clot found. Usual operation performed Transfusion with 200 c. c. of blood given

"June 12, 1931 No meningeal signs present Nystagmus to left still present No petechiae or evidence of any metastatic involvement present

"June 14, 1931 Temperature was still intermittent The child was irritable and hyperesthetic Left lower extremity was extended and resists all motion, especially at knee, where child complains of marked pain on flexion No swelling, local heat, or joint tenderness made out Child was probably localizing a purulent focus in left hip Second transfusion with 175 c. c. blood.

"June 15, 1931 Child was taken to operating room for sinus dressing Sutures were removed Swelling of cerebellar tissue in back of sinus was noticed. Dura was incised and large amount of pus obtained. Iodoform gauze was inserted

"June 18, 1931 Redressed There was a beginning definite herniation of cerebellum behind sinus into wound

"June 24, 1931 Marked swelling of left hip, definite tenderness, and fluctuation noted Incised and drained.

"June 31, 1931 Herniation of cerebellum filling the entire mastoid wound

"July 5, 1931 Hip healed Temperature, flat Mastoid wound was closed except for granulation tissue covering incision with slight pulsating cerebellar hernia behind it (Fig 1) Child discharged from hospital

"Aug 15, 1934 Child fully recovered and well except for herniation "

SUMMARY

1 The pathways of infection from the middle ear to the labyrinth, sinus, and cerebellum are discussed briefly

2 A case of suppurative middle ear infection with labyrinthitis, sinus thrombosis, and cerebellar abscess with herniation is reported

3 The presence of a hernia at the site of the mastoid wound is especially noted.

4 Plastic repair of the hernia was considered and after consultation with a neurosurgeon was decided against because of the danger of complicating meningitis

REFERENCES

- 1 Watkins Thomas and Yates Principles and Practice of Otology, p 417
- 2 Druss, J G Arch. Otolaryng 19 671, 1934

135 EASTERN PARKWAY

AN ANALYSIS OF ONE HUNDRED CASES OF ACUTE POLIOMYELITIS

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DURING the summer and fall of 1932 Philadelphia and the surrounding vicinity experienced an outbreak of acute poliomyelitis of epidemic proportion. From July to November 687 cases were reported to the Department of Public Health; of this number 100 cases were hospitalized in the Children's Hospital of Philadelphia.

Poliomyelitis in its historical, etiologic and other aspects has been presented so recently in the monograph by the International Committee for the Study of Infantile Paralysis that we are concerning ourselves in this paper with a statistical analysis only of the data available in this group of cases.

INCIDENCE

1 *Seasonal*—Chart 1, a graphic representation of the number of cases admitted to the hospital over fifteen-day periods shows that the maximum point of admission was reached in the last week of August and the first week in September. This peak is in conformity with the curve which Aycock (323)† has charted showing the seasonal distribution of poliomyelitis in the northern United States.

2 *Age*—The age of the patients in this series varies from six months to twelve years, twelve years being the upper age limit for admission to the Children's Hospital. The age distribution is graphically depicted in Chart 2. It is quite obvious that the bulk of the cases (51 per cent) lies between the ages of eighteen months and five years, with the maximum incidence at four years.

3 *Sex*—There is a very slight preponderance of males over females, 55 per cent of the patients being male; thus the ratio of male to female patients is 1.22 to 1. Of the 36,000 cases summarized by the International Committee for the Study of Poliomyelitis (407) the ratio was 1.3 to 1.

4 *Color*—In this series of 100 cases thirty-one were negroes. This percentage of negroes did not seem unusual to us since the Children's Hospital is situated in an area in which there is quite a large negro population.

From the Children's Hospital of Philadelphia and the Pediatric Department of the University of Pennsylvania.

Work on thesis for master's degree submitted to the Graduate School of Medicine, University of Pennsylvania for postgraduate work.

†Free reference has been made to the *Survey from the International Committee for the Study of Infantile Paralysis*, published by the Williams & Wilkins Company, 1932. The page references throughout this paper are to this volume.

lation and since negroes approximated 40 per cent of our total admissions in 1932. However, Armstrong in a series of 240 cases in Chicago during 1916 found only four negroes with this disease even though there was quite a large negro population in that city. From his figures one might conclude that a racial immunity exists, a conclusion not warranted from our data, nor from the data collected by the Department of Public Health.

5 *Constitutional Factors*—The state of nutrition of eighty-five patients was definitely described in our records, and, while actual weights were not noted in every case, the nutritional state was found to be good

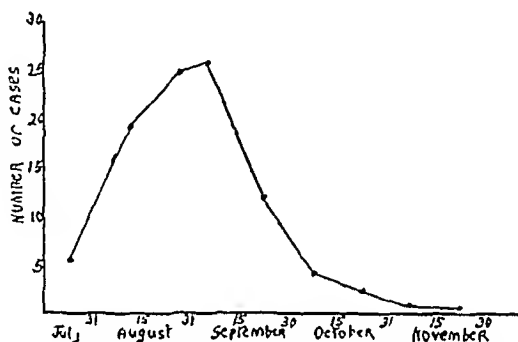


Chart 1—Seasonal distribution of poliomyelitis

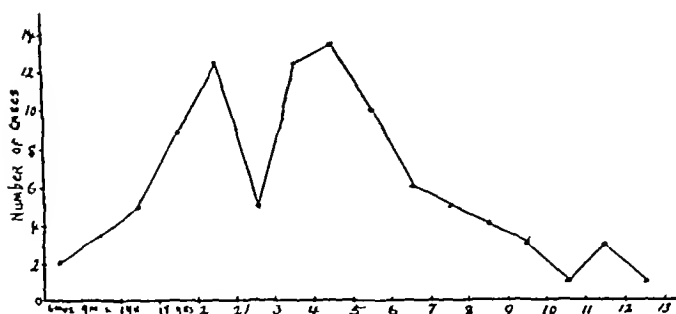


Chart 2—Age incidence.

in forty-nine cases, fair in twenty-four, and poor in twelve. This is in keeping with the observation of the early writers on poliomyelitis, who stated that it was the healthy, well-developed child who seems most susceptible to the disease.

The diet was specifically noted in eighty-five of one hundred cases. Forty-nine of this number had received a good diet, one which provided ample calories and contained a sufficient amount of protein together with an abundance of green vegetables and vitamins. Twenty-four of the eighty-five children were considered to have had a fair diet, which contained only a moderate supply of green vegetables, vitamins, and protein.

The remaining twelve patients had received a diet which was poor in these essential elements. The nutritional status as tabulated in the preceding paragraph is closely correlated to these dietary differences.

The red blood cell count was studied in seventy-six of the hundred cases. In fifty six of this number the count was between 4 and 5 millions. In twenty of the cases the red blood cell count was found to be between 3 and 4 millions. The lowest figure was 3 200,000. The percentage of hemoglobin was recorded in seventy seven cases and ranged between 75 and 100 per cent (Sanli) in fifty one cases and between 60 and 75 per cent in twenty-one cases.

It would appear from these figures that the disease did not single out the poorly fed, poorly nourished or anemic child.

6 *Blood Types*—There have been many conflicting reports concerning the susceptibility of individuals of the various blood groups to poliomyelitis. We have studied the blood types of sixty seven of our patients. From the results shown in Table I it would appear that the individuals of no one group were more susceptible to poliomyelitis than those of another.

TABLE I

INCIDENCE OF BLOOD GROUPS IN OUR SERIES OF CASES OF POLIOMYELITIS AND THE NORMAL AVERAGE IN CHILDREN'S HOSPITAL

	I	II	III	IV
Nonpolio cases (per cent)	6	40	10	45
Polio cases (per cent)	35	36.7	17.5	42

7 *Family Incidence*—Our 100 cases represented ninety two families. One case was recognized clinically in each of eighty four of these families. Two cases were found in each of six families on two occasions three cases were discovered in a family. In only eight cases was there a definite record of some other illness in the families of the patients with poliomyelitis. The nature of these illnesses was not known. It is possible that they were abortive poliomyelitis infections and that the incidence of multiple cases in families was much higher than the above figures indicate.

8 *Prophylaxis*—We shall not discuss at length the value of the various types of prophylaxis against poliomyelitis. However of the 100 cases studied, four had received citrated whole blood from a parent as a prophylactic measure. One of these four patients received 60 c.c. of whole blood intramuscularly six days before he was discovered to be suffering from poliomyelitis. Two received it ten days before the onset of the disease and in the fourth patient the disease was discovered two weeks after injection. None of these patients developed definite paralysis. It would not seem from these results that we had obtained as

complete a protection from the disease by the administration of adult blood as was found to be the case in the report of the Bradford, Pa., epidemic. It is, however, interesting that none of these four patients developed paralysis, when the incidence of paralysis in our total group was 48 per cent. Possibly the blood obtained from these adults may have had little antiviral potency.

TYPES OF CASES

In the grouping of our cases we used the classification formulated by the New York City Department of Health, which was modified by the International Committee for the Study of Infantile Paralysis (186).

Since in our series neither the abortive nor the ataxic type was recognized our cases may be grouped into one of three types, viz:

(1) *Nonparalytic Type* This group includes those cases in which no paralysis or muscle weakness was noted, but in which other clinical signs of poliomyelitis were found and spinal fluid changes were observed.

(2) *Type With Subeortical Paralysis* This group includes those patients who showed definite paralysis or weakness of the muscles supplied by the spinal or cranial nerves, thus patients in whom there was evidence of bulbar palsy are included in this group.

(3) *Encephalitic or Cerebral Type* In this group are placed those cases characterized by cerebral involvement, usually indicated by prolonged stupor, drowsiness, or convulsions.

Some of the cases were rather mixed in type, and these are classified according to their predominating symptoms.

Of our one hundred cases, fifty-two were of the nonparalytic, forty-three of the subeortical, and five of the encephalitic type.

SYMPTOMATOLOGY

It is generally agreed by all writers that the symptomatology of poliomyelitis is highly varied, and this is certainly borne out by an analysis of the present series. Chart 3 represents the incidence of the various constitutional symptoms in the 100 cases studied.

1 *General*—*Fever* In 91 per cent of the cases the temperature was found to be elevated on admission, or a very definite history of fever was obtained. The range of temperature varied considerably although seventy-two of the patients had rectal temperatures between 100° and 102° F. There were six patients in whom the temperature was above 104° F. including one whose temperature reached 107° F. Thirteen patients who gave a definite history of fever before admission were afebrile during their stay in the hospital. Only nine patients were free of fever during the entire illness, as far as we could determine. It is very possible that these children at one time or another did have some fever which escaped notice.

The duration of the fever was also quite variable, as is shown in Chart 4. In the majority of instances the febrile period was from one to four days (fifty-six cases). Sixteen patients remained febrile for a period ranging from five to nine days while one continued to have fever for eleven days, and one for sixteen days without any complicating cause. It is quite obvious that in our series the characteristic temperature curve is one with a sharp rise at the onset of the disease and an early drop by crisis. In no instance have we encountered a temperature

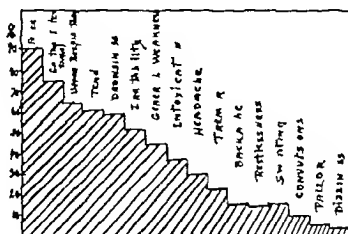


Chart 3.—Relative frequency of symptoms.

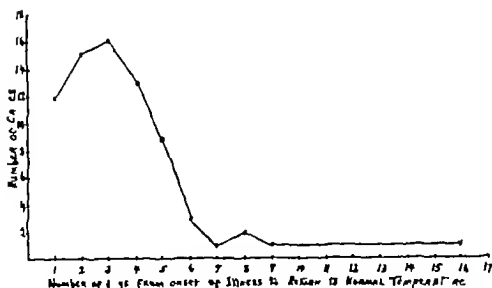


Chart 4.—Number of days from onset of illness to return to normal temperature

curve described by Draper as the 'dromedary' type. All of our febrile patients manifested the type of onset which the International Committee for the Study of Infantile Paralysis found to be the most common viz.

By far the most common type of onset is that in which the symptoms of systemic infection progressed rapidly and uninterruptedly to those indicating an involvement of the central nervous system.

Hyperesthesia. Marked tenderness was a striking finding in 63 per cent of our cases. This was elicited sometimes by active motion, sometimes by passive motion but always by deep pressure. The onset of

hyperesthesia was usually early in the disease. In the nonparalytic type this was rather a transient symptom, while in the paralytic type it was protracted.

Drowsiness This was also an early symptom found in 59 per cent of the cases. It was present in varied degrees in all three types of cases. Some patients who showed marked drowsiness made complete recoveries, whereas others exhibiting little initial drowsiness suddenly developed bulbar palsy with stupor and died.

Headache and Backache These symptoms were of relatively low incidence in the total group (Chart 3), but in children over two and one-half years of age, who were hence able to localize their pain, the incidence was greater. In this latter group, headache occurred in 46.6 per cent and backache in 26.6 per cent.

Irritability, weakness, and tremor, were rather frequent. Restlessness and sweating occurred occasionally. Convulsions developed in 10 per cent of the cases.

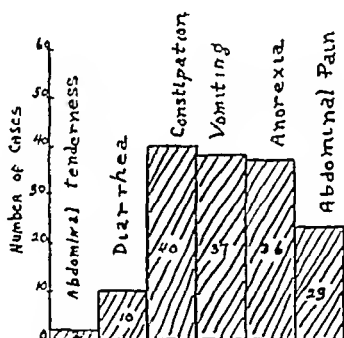


Chart 5—Gastrointestinal symptoms

2 Gastrointestinal—Symptoms referable to the gastrointestinal tract were noted in 73 per cent of the cases. As can be seen from Chart 5, constipation, nausea, and vomiting were most common. Anorexia, which occurs so often in all febrile diseases, was also common here. The frequency of abdominal pain was surprisingly high, and because of its severity a number of these patients were very carefully observed for an acute surgical abdominal condition. This pain was often localized in the rectus muscles. At times it was unilateral, and at other times, bilateral. It was accompanied by hyperesthesia in the involved area. Definite rigidity was lacking.

3 Respiratory—Definite symptoms and signs of respiratory infection were noted in 67 per cent of the patients, although a history of sore throats and coryza was obtained in only nine, and a history of cough, in seven. The great frequency of infection in the nasopharynx in poliomyelitis is clearly indicated by the accompanying Chart 6.

Sixteen of the patients showed evidences of respiratory embarrassment. In every case the dyspnea was accounted for either by bulbar paralysis or by paralysis or weakness of the intercostal muscles or diaphragm. When the dyspnea was due to bulbar palsy, it was constant and required the uninterrupted use of the respirator. Dyspnea caused by paralysis of both the diaphragm and intercostal muscles was also constant. In those cases in which either the intercostal muscles or the diaphragm alone were weak or paralyzed, the dyspnea was intermittent and was less severe. Cyanosis accompanied the dyspnea in six of the sixteen patients. None of our patients gave any evidence of cardiac damage attributable to poliomyelitis. Two of the patients were discovered to have systolic murmurs, but without any associated cardiac enlargement. These murmurs were considered to be functional in nature.

4 Nervous System.—Chart 7 shows the frequency of such disorders

While full or bulging fontanel was found in only four cases, these represent 50 per cent of the patients under one year of age. Whenever

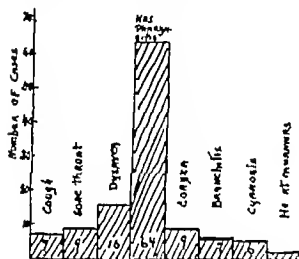


Chart 6.—Cardiorespiratory symptoms.

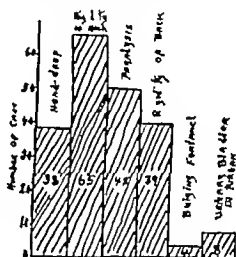


Chart 7.—Nervous symptoms.

there was rigidity of the back, there was also true rigidity of the neck. The frequency of a positive Kernig sign was not recorded because in the treatment of our patients serum was injected into the gluteus muscles immediately after admission, making this sign wholly unreliable. Some patients showed trophic disturbance resulting from pressure. Many showed vasomotor imbalance as evidenced by a tachycardia, mottling of the skin and coldness of the extremities with cyanosis. Catatonia was seen in two cases. With the drowsiness and hyperesthesia, as listed under the general symptoms, the patients often presented most confusing pictures for differential diagnosis. The nervous manifestations frequently resembled those seen in other diseases. For instance, a case of tuberculous meningitis was suspected of being poliomyelitis for several days, and two cases of bacillary dysentery, because of their central nervous system symptoms were treated as poliomyelitis until the characteristic stools appeared.

TABLE II
DISTRIBUTION OF PARALYSIS

	CASES
Both legs	10
One leg (2 right, 5 left)	7
Both legs and both arms	4
Both legs and one arm	4
One arm (3 right, 4 left)	7
One arm and one leg, same side (right)	2
One arm and one leg, opposite sides	1
Both arms	1
Both arms and 1 leg	0
Girdle	
Abdominal muscles, 11	
Diaphragm and intercostal muscles, 6	17
*Cranial nerves	12

*We have substituted this heading for the one which Lovett calls Facial Alone. These cranial nerve palsies were distributed among the various nerves as follows

Oculomotor	5
Facial	5
Oculomotor and Optic (Child appeared not to see however ophthalmoscopic examination was negative)	1
Glossopharyngeal	4
Glossopharyngeal pneumogastric, and facial	1
Glossopharyngeal pneumogastric, and oculomotor	2

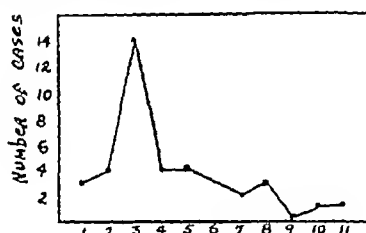


Chart 8—Relation of onset of paralysis to day of illness

6 *Genitourinary System*—The one disorder recorded was retention of urine, which occurred in nine cases, being present only in the acute stage of the disease and clearing spontaneously

7 *Glandular System*—No case of cervical or other lymph node enlargement was recorded. In no instance was the spleen noticeably enlarged

8 *Paralysis*—Incidence Of the 100 cases constituting this series, forty-eight developed definite paralysis

Interval Between Onset and Paralysis In forty cases we have been able to establish this time interval. The average duration was 4.15 days (Chart 8). In only two patients of this group did paralysis occur on the first day of the disease. The frequently described and dramatic picture of a previously healthy child awaking in the morning with paralysis was not observed in our group. There seemed in each instance to have been some prodromal symptoms. In the majority of our cases, paralysis occurred on the third day of illness. In several instances the paralysis seemed to be of a progressive nature, not reaching its max-

imum for several days. It appeared that as long as an elevation of temperature persisted there was a possibility of the paralysis extending to heretofore uninvolved muscles. We were much impressed by the frequency with which orthopedic examinations detected mild degrees of muscular weakness which had been entirely overlooked during the routine observations.

Distribution of Paralysis In this presentation we are following the classification of distribution adopted by Lovett

TABLE III
MUSCLE GROUP PARALYZED

	MUSCLE GROUP	CASES
Shoulder	All	8
	Abductors	22
	Adductors	18
Upper Arm	All	5
	Extensors	10
	Flexors	3
Forearm	All	4
	Extensors	3
	Flexors	2
	Pronators	1
	Supinators	1
Hand	All	4
	Extensors	3
	Flexors	2
	Abductors	2
Hip	Adductors	1
	All	17
	Abductors	14
	Extensors	11
	Adductors	11
Thigh	Flexors	5
	All	17
	Abductors	16
	Extensors	16
	Flexors	5
Leg	Adductors	5
	All	16
	Flexors	14
	Extensors	11
	Abductors	9
Foot	Adductors	6
	All	16
	Flexors	12
	Abductors	9
	Adductors	6
	Extensors	3

In Table III, a summary, we are recording the various muscle groups involved in the paralysis. Our figures are in accord with those of Lovett, who found that one or both legs were the parts most frequently involved. The incidence of cranial nerve involvement in our group (12 per cent) is in striking agreement with that reported in the series of Ruhrah and Mayer (177). While abdominal muscle paralysis occurred in 72 per cent of a series cited by the International Committee (173), only 23 per cent of our paralyzed patients had involvement of the abdominal wall musculature.

Reflexes In the ninety-three patients on whom we have data, the reflex changes were as follows:

(a) Twenty-six showed no reflex changes at any time during their illness, none of these cases developed any palsy.

(b) Sixty-seven patients exhibited reflex abnormalities, either hyperactivity, hypoactivity, or loss of the reflexes. Of these sixty-seven, nineteen did not develop paralysis. Table IV shows the types and distribution of the reflex abnormalities in these nineteen cases.

TABLE IV

TYPES OF ABNORMAL REFLEXES IN 19 PATIENTS WHO DID NOT DEVELOP PARALYSIS

PATIENT	PATELLAR	ACHILLES'	CREMASTERIC	ABDOMINAL	TRICEPS	BICEPS	PUPIL-LARY
F K	Absent	Absent	Absent	Hyper Absent	Hyper	Hyper	
A Z	Hyper	Hyper					
D S	Absent	Absent					
M R.	Absent						
J B	Absent	Absent					
C S	Absent	Absent					
J C	Hyper		Hyper Absent Diminished Hyper Hyper Hyper Absent	Hyper	Hyper		
R E	Hyper	Absent					
E S	Diminished						
E S	Hyper	Hyper					
W B	Absent	Absent					
E M	Absent	Absent					
D G	Hyper	Hyper					
E M	Diminished						
H M				Diminished	Hyper	Hyper	
M B	Diminished	Diminished	Absent	Absent Absent			
J D							
R G							
D L	Absent	Absent					

From these data we conclude that one cannot predict with certainty by the status of the reflexes whether or not a patient will develop paralysis, except in those instances where normal reflexes are present. We were unable to establish the time relationships between the development of abnormal reflexes and the onset of paralysis.

LABORATORY DATA

1 *Spinal Fluid*—The spinal fluid of ninety-six patients was studied. The first spinal fluid was obtained immediately after admission to the

hospital, and in thirty nine cases a second, and sometimes a third, examination was made during the course of the disease. In every case the spinal fluid was examined within an hour after the lumbar puncture

Gross Appearance The spinal fluid obtained by lumbar puncture was opalescent in eleven cases and clear in eighty five

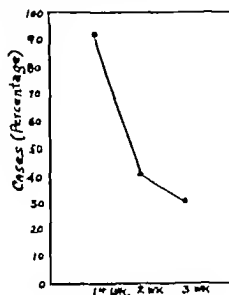


Chart 9—Percentage of cases showing elevated spinal fluid cell counts with relation to week of illness.

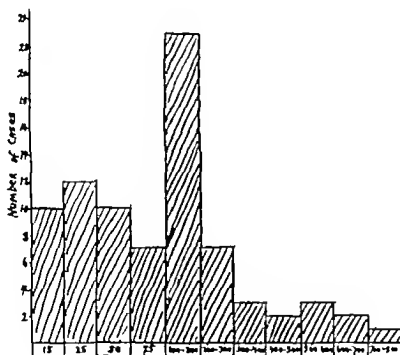


Chart 10—Spinal fluid white cell counts (per c. mm.)

Cell Count The spinal fluid cell count made during the first week following onset was found to be elevated in most instances. Of the eighty two cases studied in this period only seven did not have a cell count above the normal limits. Our laboratories accept the upper limit of normal to be ten cells per cubic millimeter. One of these seven patients showed an increase on subsequent examination. Other patients in subsequent punctures also showed increases beyond their first counts. Spec

mens obtained between seven and fifteen days following the beginning of the disease were very much less likely to show pleocytosis. Only ten of twenty-three patients during the second week exhibited an abnormal number of cells in their spinal fluid. When the spinal fluid was studied two or more weeks after onset, only eleven out of thirty-five patients showed an increase in the number of cells. This is graphically shown in Chart 9, which illustrates the tendency of the spinal fluid to return to normal with the subsidence of the active period of the disease. The actual degree of pleocytosis varied widely. However, the majority of our cases had spinal fluid cell counts above 100, as can be seen from Chart 10. The highest figure reported was 740 cells per cubic millimeter. In general the increase in the spinal fluid cell count was due to a rise in the number of lymphocytes. However, in many instances there were also considerable numbers of polymorphonuclear cells found. The polymorphonuclear response was much more frequent in the early days of the disease than in the later stages. It is sometimes said that early in the disease the spinal fluid response is a polymorphonuclear one and that later in the disease the response is lymphocytic. This was found to be true in only 18 per cent of the cases in our series. Twenty per cent of the differential counts made on spinal fluid obtained after three weeks of the illness still showed some polymorphonuclear cells. We are led to the conclusion that the presence of polymorphonuclear cells in the spinal fluid is not associated with any particular period of the disease but that they are found in large numbers only in the early stages. In addition to the lymphocytes and polymorphonuclear cells, endothelial cells were occasionally found in the spinal fluid. Frequently degenerated cells were found in the spinal fluid, even when the examination was performed immediately after the fluid was obtained. It was usually impossible to determine the nature of such cells, and their significance is unknown. The differential counts were usually made on centrifuged specimens stained with methylene blue.

Study of the spinal fluid cell counts seen made it apparent that a high count did not necessarily mean a severe illness. On the contrary, the reverse is suggested from our findings. As can be seen from Chart 11, paralysis occurred less frequently when the cell count was above 300 per cubic millimeter than when it was below this figure. The patients showing evidences of meningeal irritation usually had a high cell count with the polymorphonuclear cell predominating.

There were eighty-six patients with a cell count below 300 in the first fluid obtained. Of these, forty-four (52 per cent) exhibited detectable paralysis. Ten patients had more than 300 cells, and of these patients only two became paralyzed (20 per cent). Despite the fact that this latter group consisted of so few cases, we are inclined to attach importance to these figures.

Globulin The spinal fluid of eighty three patients was examined for globulin the examination was made by adding a few drops of a saturated aqueous solution of ammonium sulphate to the fluid. The globulin was considered to be increased when this test produced a cloddiness which is proportional to the amount of globulin present. Of these eighty three spinal fluids, seventy seven showed an increase in globulin content. The amount of globulin increase did not bear any definite relationship to the number of cells in the spinal fluid. Sometimes the globulin was increased when no cells were found, while in other instances there was only a slightly increased globulin content in the presence of a high cell count. The change in globulin content persisted longer than any of the other abnormalities noted in the spinal fluid

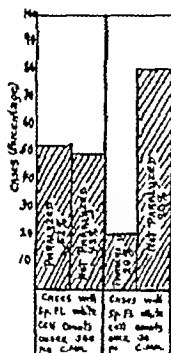


Chart 11

in many cases an increase in the globulin was present after all other pathologic findings had disappeared.

Sugar Quantitative sugar estimations were carried out on 104 samples of spinal fluid. Twenty three per cent of these determinations were found to be elevated above 72 mg per cent which was considered to be the highest normal figure. In no case was there any decrease in the spinal fluid sugar. There was no definite relationship between the changes in sugar content and the various other spinal fluid changes.

Chloride Content This was determined in 100 cases. In only four instances was there any reduction below 650 mg per cent (as Cl) which was considered the lowest normal value. The spinal fluid of the remaining ninety six cases showed a chloride content very close to 700 mg per cent.

Pressure Spinal fluid pressure readings were reported in most of the cases and showed wide variations. In general a moderate elevation

of pressure was found. However, because of the inaccuracies which are inevitable in the measurement of spinal pressure in children, due to their struggling, little significance can be attached to any detailed analysis of these findings. In no case was the spinal fluid pressure high enough to be considered dangerous per se.

Wassermann Reaction The spinal fluid Wassermann reaction was carried out in twenty-five cases and was found to be negative in all of them.

Pellicle Formation A very slight pellicle was formed in nine spinal fluid samples after they were allowed to stand.

2 Urine—Seventeen patients showed a "trace" or "faint trace" of albumin in the urine. Fourteen children who had been vomiting or whose fluid intake had been insufficient were found to have ketonuria. The urine of two children contained granular casts on one or two occasions.

3 Serology—The blood Wassermann reactions of twenty-four of our patients were recorded. Twenty-three were negative, one was positive. Two of the twenty-four patients were attending our clinic for anti-syphilitic treatment. The positive Wassermann found was in one of those two children.

4 Hematologic Findings—The hemoglobin and erythrocyte findings have already been discussed. We obtained white blood cell counts in seventy-one cases and differential counts in seventy-nine. These counts were all made on the day of admission and therefore in the acute stage of the disease.

Table V summarizes these findings.

TABLE V
TOTAL WHITE COUNTS

CASES	THOUSANDS
15	From 5 to 7
32	From 7 to 10
28	From 10 to 15
4	Above 15

DIFFERENTIAL WHITE COUNTS

UNDER THREE YEARS OF AGE				OVER THREE YEARS OF AGE			
I Polynuclears	Normal	(45-55%)	18	I Polynuclears	Normal	(55-65%)	20
	Increased	(> 55%)	17		Increased	(> 65%)	11
	Decreased	(< 45%)	5		Decreased	(< 55%)	8
II Lymphocytes	Normal	(40-50%)	18	II Lymphocytes	Normal	(35-45%)	17
	Increased	(> 50%)	5		Increased	(> 45%)	7
	Decreased	(< 40%)	17		Decreased	(< 35%)	15

MORTALITY

Seven deaths occurred in our 100 cases. A brief summary of these seven cases follows. Three of these patients were under eighteen months

of age. Since there were twelve patients in our entire series under that age, the mortality rate in the patients of this age group was 25 per cent. This high mortality during infancy is in keeping with that reported by other observers (352-353)

TABLE VI
FATAL CASES

	AGE	SEX	RACE	DAYS OF ILLNESS	TYPE OF CASE
D R.	6 mo.	F	Black	Died on 9th day four days after admission.	Subcortical first then encephalitic symptoms developed
A P	9 mo	M	White	Died on 5th day, day after admission.	Subcortical also encephalitic symptoms. Never regained consciousness.
L B.	15 mo.	F	White	Died on 6th day, day after admission.	Subcortical—paralysis of pharyngeal and laryngeal muscles.
E N	30 mo.	F	White	Died on 5th day day of admission.	Subcortical—paralysis of larynx and pharynx. Encephalitic symptoms.
M S	3 yr	F	White	Died on 4th day, day of admission.	Subcortical—paralysis of larynx and pharynx. Died in respirator
D G	5 yr	F	Black	Died on 4th day, day of admission.	Encephalitic
D O	11 yr	M	White	Died on 8th day, two days after admission.	Subcortical—paralysis of larynx and pharynx. Died in respirator

CLINICAL PICTURE

One gathers from the data presented how difficult it would be to reconstruct a typical case of poliomyelitis. There was no one sign pathognomonic of this disease. However, the occurrence of certain of the more classical symptoms in a patient would suggest such a diagnosis. No symptom or sign noted in our series was present in every case. About 10 per cent had no fever. Seven of the eighty-two patients whose spinal fluids were examined had normal cell counts and six of these showed no increase of the globulin content.

The more important symptoms to be elicited are moderate fever as associated with upper respiratory tract infection, gastrointestinal symptoms, muscular weakness, and a feeling of malaise. The more common gastrointestinal symptoms to be expected are anorexia, nausea, vomiting and constipation in other words, disturbances of the gastrointestinal tract which are usually found in most of the infections of childhood. The malaise may be of a moderate degree or so profound as to leave the patient in a state of complete exhaustion. Profuse sweating is common in this latter state. This severe degree of intoxication was seen only in the early part of the disease. In many in

stances, because of the marked generalized muscular relaxation, it was impossible during this stage to determine the extent of paralysis. With recovery from this acute exhaustion, it was often discovered that no true paralysis had existed. Headache and backache are commonly present. The patient may be either drowsy or irritable. At times the irritability is noticed only when the patient is disturbed. Early in the disease hyperesthesia is a common complaint. This may be generalized or limited to the spine but most commonly is in regions where paralysis is later to occur. Muscular tenderness is sometimes brought out by passive motion when there is no complaint of pain. In the nonparalytic cases hyperesthesia is of a more transient nature.

In the diagnosis of poliomyelitis there are several points in the physical examination that are of extreme importance. Hyperesthesia, as described above, is frequent. Alteration of the reflexes is found in the majority of instances. However, this is not always associated with paralysis even though the reflex may be entirely absent. Palsy is not likely to develop in the absence of reflex changes. Stiff neck is an early and frequent sign. Associated with this in about half the cases one finds a head drop, which can be detected by elevating the patient's shoulders while he is flat on his back. When head drop is present, the patient is unable to bring his head up from the bed or does so very weakly. This symptom we have found to be of considerable help in detecting some of the more obscure cases. Stiffness of the back associated with pain on flexion is also an early symptom in a large number of cases. This can be demonstrated by having the patient sit on a bed with his feet extended and having him flex his trunk bringing his head toward his legs. The average normal child can almost touch his legs with his head while in this position.

Muscular paralysis, which may be limited to a single muscle group or which may be so extensive as to involve the entire body, is the most classical sign. However, it is to be remembered that over half of the patients do not develop paralysis. In fact, all the neuromuscular symptoms may be absent. In many of the cases the paralysis comes on suddenly and is complete. In other cases it is progressive over several days, in these latter cases there is usually a continued fever. As long as the fever continues, it is possible that the paralysis may spread. The localization of the paralysis differs in different epidemics. The more usual localization is in the legs. Cranial nerve palsy is sometimes found. The more common of these are the oculomotor, the facial, and the spinal accessory. Other central nervous system symptoms are occasionally encountered, such as convulsions, respiratory disturbances, and disturbances of swallowing.

The chief diagnostic laboratory aid is obtained from examination of the spinal fluid, which is characterized by an increased globulin content and cell count. Early in the disease the predominating cell may be a

polynuclear cell. Soon however lymphocytes predominate. The average count is between 75 and 200. However, there is considerable variation. As mentioned above, a normal spinal fluid may be present. In the majority of instances the fluid is colorless and clear, but occasionally it is opalescent.

The white blood cell count shows a slight increase averaging around 10 000, occasionally over 15 000 and often under 7 000. The differential count shows the polynuclear cells slightly increased.

TREATMENT

In addition to the symptomatic treatment administered to each of these cases e.g., hypertonic solutions intravenously to patients exhibiting encephalitic symptoms sedatives, etc., the majority of the patients received a blood transfusion and serum on admission. The serum, obtained from the Philadelphia Department of Public Health, was either contact or convalescent. It was not tested for its antiviral potency. Blood was obtained from parents. Serum was always given intramuscularly except in two instances when it was injected intravenously. The number of patients receiving serum therapy is given in Table VII. We

TABLE VII

TREATMENT	NO. RECEIVING THERAPY
Transfusion (indirect)	40
Nonparalyzed	20
Paralyzed	20
Serum	78
Nonparalyzed	30
Paralyzed	34
Average dose of convalescent serum	36.7 c.c.
Average dose of contact serum	30.6 c.c.

Some of these patients also received a blood transfusion.

are unable to evaluate the worth of this form of therapy since no effort was made to control its administration blood and serum being given to paralyzed and nonparalyzed patients alike. However in eleven cases (Table VIII) convalescent and contact serum plus the administration of an intravenous blood transfusion in the preparalytic stage of the disease did not prevent the development of paralysis. Two of these patients showed mild weakness before serum was given but developed further paralysis after treatment. The fact that five of these patients had treatment for at least four days before the paralysis developed again raises the question whether the use of convalescent serum after or very shortly before the onset of the disease is of any benefit. Of course these particular serums may have had only little antiviral potency. The orthopedic aspect of the treatment will not be discussed in this paper.

TABLE VIII

OCCURRENCE OF PARALYSIS FOLLOWING SERUM THERAPY IN THE PREPARALYTIC STAGE OF DISEASE

	O C OF CON VALESCENT SERUM	C C OF CON TACT SERUM	BLOOD TRANS	PARALYSIS DEVELOPED	
				DAYS AFTER ADMINISTRA TION	DAYS AFTER ONSET OF DIS EASE
B H	25	50	Blood trans	2	3
R M	25	40	Blood trans	5	8
P B	10	45	Blood trans	5	6
W G	40	10	Blood trans	5	7
J S	50	--	Blood trans	5	8
R C	20	40	Blood trans	2	7
J A	45	20	Blood trans	3	6
W B	25	30	Blood trans	1	4
W B	--	50	Blood trans	2	3
M G	20	40	Blood trans	1	4
M C	50	40	Blood trans	4	8

The prophylactic use of serum in the treatment of poliomyelitis is discussed in another paper published from this clinic

SUMMARY

1 An analysis is presented of the data taken from the records of 100 cases of acute poliomyelitis

2 The maximum number of patients were hospitalized during the last week of August and the first week of September, 1932 With the ages of the patients varying from one to twelve years, 51 per cent of the patients were between one and one-half and five years of age Males predominated over females in the ratio of 1.22 to 1 Color did not seem to confer any immunity The majority of the patients in this series were well-nourished, well-developed children with normal hemoglobin concentration The blood types of the patients had no influence on the incidence Four patients who had received intramuscular whole blood as an attempted prophylactic measure did not develop paralysis but did develop the disease

3 A discussion of the classification of the types of cases is presented.

4 Symptoms

A Fever Most patients exhibited fever on admission, ranging between 100° and 102° F The dromedary type of temperature curve was not encountered.

B Gastrointestinal Constipation, nausea, vomiting, and anorexia were frequent symptoms Abdominal pain was not uncommon Diarrhea of a mild type occurred occasionally

C Cardiorespiratory An initial upper respiratory infection occurred in a high percentage of cases Respiratory phenomena incident to paralysis are discussed Cardiovascular abnormalities were present

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R C	20	40	Blood trans	2	7
J A	45	20	Blood trans	3	6
W B	25	30	Blood trans	1	4
W B	--	50	Blood trans	2	3
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CLINICAL EXPERIENCE WITH CRYSTALLINE VITAMIN D THE INFLUENCE OF THE MENSTRUUM ON THE EFFECTIVENESS OF THE ANTIRACHITIC FACTOR

J M LEWIS, M D
NEW YORK, N Y

IN 1931, Askew and his colleagues¹ in England and Windaus and his coworkers² in Germany, employing different chemical methods, finally isolated from irradiated ergosterol a pure crystalline substance which has marked antirachitic activity. Windaus named this crystalline product "vitamin D₂," and the English investigators called it "calciferol." It has been fairly well established that vitamin D₂ and calciferol are identical substances, and we shall refer to them in this paper as "crystalline vitamin D." Windaus and Leuttringhaus³ have isolated a number of other substances which occur during the course of irradiation of ergosterol, and it is interesting to note that none of them has any antirachitic activity. They are all isomers of ergosterol and have been designated as "lumisterol," "tachysterol," "suprasterol 1 and 2," and "substance 248" (toxisterol).

One milligram of crystalline vitamin D has a potency of 40,000 international units (approximately 14,815 Steenbock units). Crystalline vitamin D, being an isomer of ergosterol, has the chemical formula of C₂₈H₄₄O. It is dextrorotatory and has a melting point of 114° to 115° C and an intense absorption band at 265 mμ. The pure vitamin is extraordinarily stable, being resistant to oxidation and showing no loss of potency after storage for five months at 20° and at 37° C or after heating for nine hours at 115° C.

Crystalline vitamin D as well as tachysterol and substance 248 are toxic to rats and mice when given in large amounts. The margin of safety, however, is great, inasmuch as toxic effects occur only after the administration of 3,000 times the therapeutic dose of crystalline vitamin D.

Clinical tests of the antirachitic value of crystalline vitamin D have been carried out abroad by Spence⁴ and by Gorter.⁵ Spence observed the effect of the daily administration of 1 c.c., 2 c.c. and 3 c.c. of an oily solution of crystalline vitamin D on the course of the disease in twelve patients with active rickets, ranging in age from one to eighteen years. One cubic centimeter of this preparation contained 3,000 international units (1,111 Steenbock units). In all

From the Department of Pediatrics New York University

This work was planned with Dr. A. F. Hess but was carried out and written after his death.

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week It should be added that only those babies whose mothers were cooperative and could be relied upon to follow instructions were included in the study

After the infants had received crystalline vitamin D in milk or in oil for four weeks, roentgenograms were again taken of their wrists in order to determine the degree of healing which had taken place during this period As emphasized in previous publications, the employment of the four-week test period is a good method of evaluating the relative potencies of antirachitic agents In order to determine the progress of healing, however, roentgenograms were taken, when possible, after the infants had received crystalline vitamin D for six, eight, and ten weeks

If milk were found to play a rôle in bringing about better utilization of the antirachitic factor, it would be of interest to know the minimum curative dose of crystalline vitamin D incorporated in milk Thus we might learn whether milk to which the antirachitic factor has been directly added resembles, from the point of view of the number of units required to cure rickets, irradiated milk or milk from cows fed irradiated yeast Accordingly, eight rachitic infants were given daily 45 units of crystalline vitamin D incorporated in 24 ounces of milk, a potency which is known to be adequate for irradiated milk but inadequate for "yeast" milk

The scope of the investigation was further enlarged to determine the effect on the course of active rickets of a larger amount of crystalline vitamin D dissolved in oil Ten rachitic infants were therefore given daily 6 drops of an oily preparation of crystalline vitamin D totaling 900 Steenbock units

This study therefore comprised thirty-six rachitic infants divided into four groups (1) nine infants receiving daily 90 units of crystalline vitamin D dissolved in oil, (2) nine infants receiving 90 units incorporated in milk, (3) eight infants receiving 45 units of crystalline vitamin D incorporated in milk, and (4) ten infants receiving 900 units of crystalline vitamin D dissolved in oil

The incorporation of crystalline vitamin D in milk was accomplished either by (1) the "vipro" process, as advocated by Laquer,⁷ consisting of the addition of an oily preparation of vitamin D to dry skimmed milk which is then mixed with fluid milk, or (2) by dissolving crystalline vitamin D in propylene glycol* and adding this solution directly to milk By means of these methods, crystalline vitamin D is uni-

*Hunt (J Indus. & Engin. Chem 24 361 1932) has shown propylene glycol to be relatively nontoxic and states that it may have a true food value in the sense that ethyl alcohol does without the drug action of the latter Young rats grew at the normal rate and reached maturity when the only liquid they received was a 5 per cent solution of propylene glycol It was also well tolerated by animals whose livers and kidneys had been injured by various poisons

Propylene glycol is miscible with milk and water in all proportions and forms stable solutions of crystalline vitamin D The taste and odor of milk are not altered by the addition of therapeutic amounts of crystalline vitamin D propylene glycol solution.

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formly distributed throughout the milk, a fact which has been demonstrated by biologic assays of various levels of milks so treated. The *vipro* method was used for the preparation of milk of weaker potency namely 45 units in 24 ounces of milk, and the propylene glycol solution for the incorporation of 90 units of crystalline vitamin D in 24 ounces of milk. The practical advantage of a propylene glycol solution of crystalline vitamin D is that it mixes freely with the milk whereas drops of an oily solution cannot be distributed uniformly through milk unless the *vipro* process is employed.

The preparations of crystalline vitamin D were kindly sent to us by Dr. Charles W. Hooper. The incorporation of crystalline vitamin D was carried out daily shortly before delivery of the milk. Biologic assays of the milk and of the oily preparations of crystalline vitamin D used in this investigation were made three times during the course of the investigation, and the results showed that the requisite number of units were contained therein.

RESULTS

The results of this study may be gleaned from Table I. In surveying the data, it will be noted that at the end of four weeks all of the nine rachitic infants receiving daily 90 units of crystalline vitamin D in milk showed definite healing, whereas only three of nine rachitic infants receiving 90 units of crystalline vitamin D in corn oil showed healing. It should be added that the gains in weight in both groups were approximately the same.

At the end of six weeks healing progressed in those infants receiving the antirachitic vitamin in milk, and in one instance the lower ends of the radius and ulna were normal. We were able to obtain roentgenograms of six infants who had received crystalline vitamin D in milk for eight weeks, and in four of them the bones were normal, and in the other two infants rickets was either healed or almost healed (Figs. 1, 2, 3, 4). In contrast to these favorable results with crystalline vitamin D in milk, three of the eight infants receiving daily 90 units of crystalline vitamin D in oil for six weeks showed no healing, and at the end of eight weeks the rachitic process became worse in two instances (Figs. 5, 6, 7).

One rachitic infant (B. R.) is of especial interest and significance. This baby had received 90 units of crystalline vitamin D in oil for four weeks, and roentgenographic examination at the end of this period showed that the rachitic process advanced. This infant was then given the same number of units of crystalline vitamin D in milk and, as will be noted in Fig. 8, definite healing resulted in four weeks and calcification in the rachitic zone was increased two weeks later.

It is obvious that 90 units of crystalline vitamin D in the form of propylene glycol solution incorporated in milk was much more ef-

TABLE I
COMPARISON OF HEALING, AMONG 36 RACHITIC INFANTS, BROUGHT ABOUT BY CRYSTALLINE VITAMIN D INCORPORATED IN MILK OR IN CORN OIL

CASE	AGE (MO)	DATE BEGUN	MENSTRUUM IN WHICH CRYSTAL LINE VITA MIN D WAS INCOR PORATED	NO OF RAT UNITS (STEEN BOOK) GIVEN	ROENTGENOLOGIC RICKETS					COMMENT
					AT ONSET	HEALING AFTER 4 WK	HEALING AFTER 6 WK	HEALING AFTER 8 WK	HEALING AFTER 10 WK	
C M	8	1/23	Milk†	45	Moderate	+	++	++	+++	Porto Rican
B G	6	1/25			Moderate	+	++	++	++±	Porto Rican
F S	13	1/26			Moderate	0	0	0	++±	Negro
E D	6	2/7			Slight	+	++	++±	+++	Italian
G N	8	2/18			Moderate	+	++	++	+++	Porto Rican
C W	22	2/17			Marked	++	++	++	+++	Negro
G B	8	2/21			Moderate	++	++	++±	+++	Negro
J N	6	2/24			Mild	0	0	0 (worse)	0	Negro
V L	6	1/13	Milk†	90	Slight	++	++	Normal	+++	Italian
S Q	4	1/13			Moderate	++	++	++±	+++	Porto Rican
J A	5	1/13			Slight	+++	+++	Normal	Normal*	Negro
R L	5	1/19			Moderate	+++	Normal	Normal	Normal	Negro
C H	20	1/25			Marked	+++	+++	+++	Normal	Negro—1/25 calcium, 9.8 mg, phos phorus, 3 mg 2/23 calcium, 10.6 mg, phosphorus, 5 mg
K S	4	2/22			Slight	++	++	Normal	Normal	Negro
B O	7	3/2			Moderate	+	++	++	++	Porto Rican
F S	15	3/17			Moderate	+	++	++	++	Negro
B R	6	3/17			Moderate	++	++	++	++	Thus infant had received 90 units of crystalline vitamin D in oil for one month, and no healing re- sulted

*Denotes slight healing, ++, moderate healing, +++, marked healing, +++++, healed rickets.

* X-ray picture taken at 13 weeks

†One liter contained 60 units

‡One liter contained 120 units.

fective than the same number of units in oil. These results clearly indicate that the medium of milk allows for better utilization of the

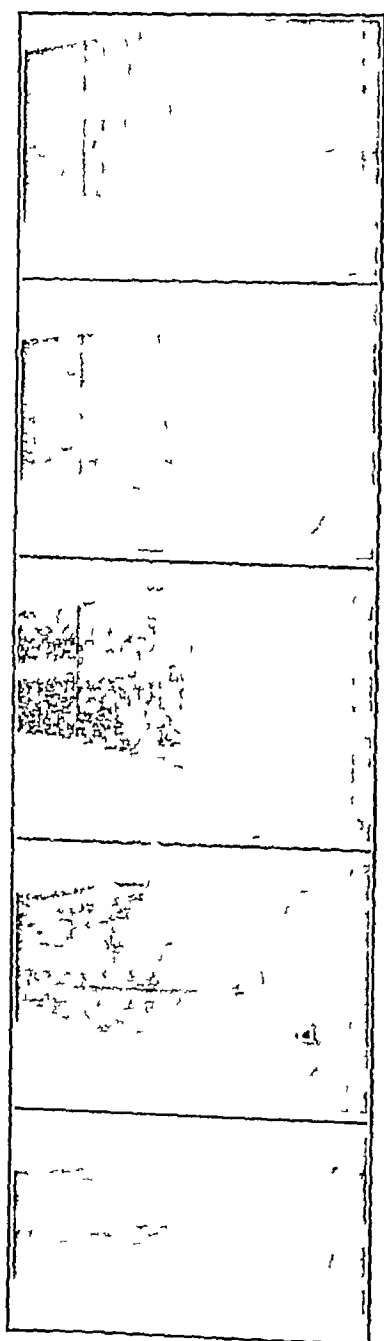


Fig 1—(C. H.) Healing of rickets brought about by crystalline vitamin D (90 units) in milk. A, January 25 (begun); B, February 21 (four weeks later); C, March 8 (two weeks later); D, March 21 (two weeks later); E, April 24 (five weeks later).

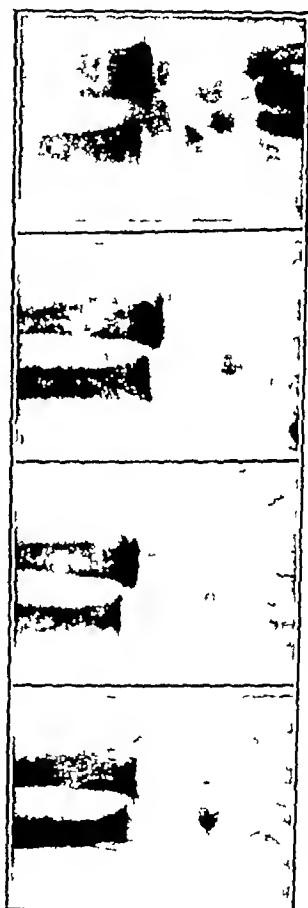
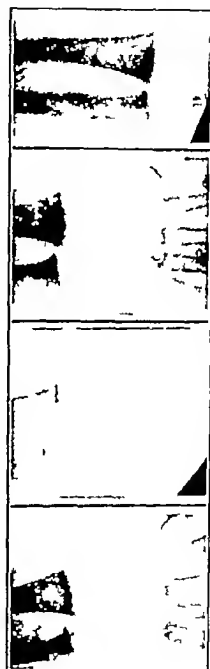
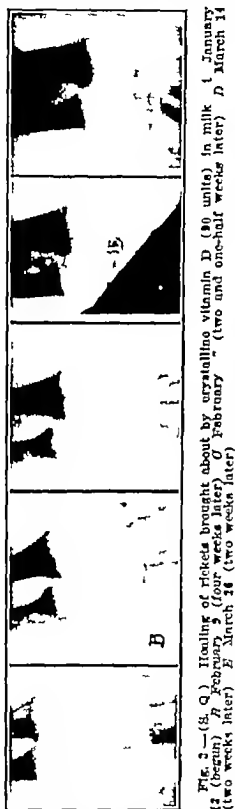


Fig 2—(R. L.) Healing of rickets brought about by crystalline vitamin D (90 units) in milk. A, January 19 (begun); B, February 15 (four weeks later); C, March 29 (three and one-half weeks later); D, April 15 (four weeks later).

antirachitic vitamin than does the medium of corn oil, and thus offer an explanation for the greater effectiveness, from the standpoint of rat units, of antirachitic milks as a group as compared with viosterol

Of the eight infants who received daily 45 units of crystalline vitamin D in 24 ounces of milk, six showed definite healing at the end of four weeks. At six weeks healing progressed in these six infants, and after eight weeks roentgenographic examination revealed further



healing, in two instances the rachitic disorder was almost healed. Two infants, however, failed to show healing at the end of four and six weeks, and in one infant followed for eight weeks the rickets became worse. One baby (F S) who showed no healing after having received 45 units in milk for six weeks, was given 90 units in milk for

four weeks, and at the end of this period definite healing was noted on the roentgenogram

It is evident that the results with 45 units of crystalline vitamin D in milk were superior to those obtained with 90 units of crystalline

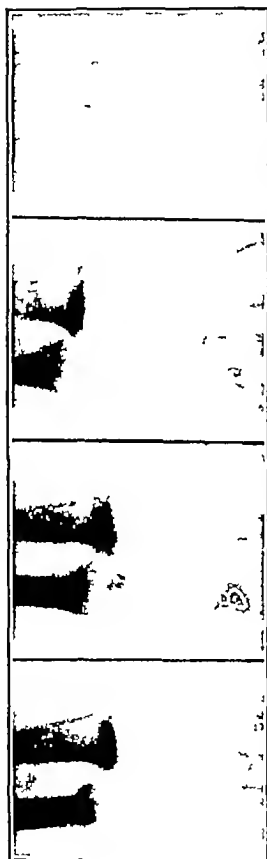


Fig 5—(C, B) Absence of healing with crystalline vitamin D (90 units) in corn oil. A, February 28 (begun) B, March 29 (four weeks later) C, April 12 (two weeks later) D, April 27 (two weeks later)

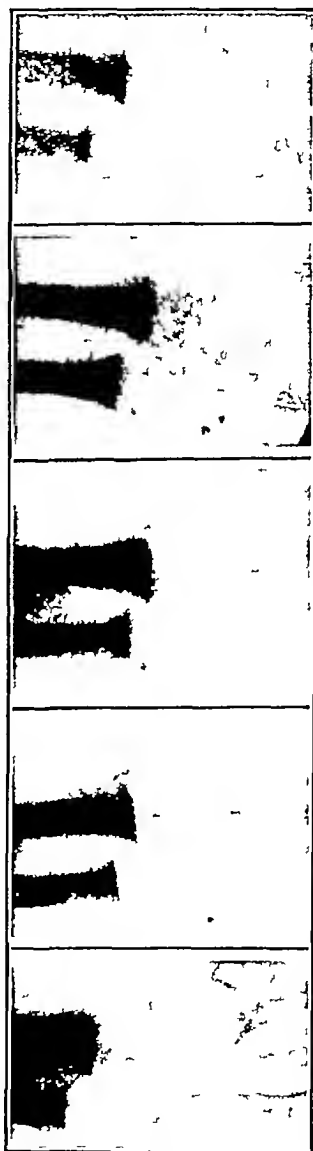


Fig 6—(D, E) Absence of healing with crystalline vitamin D (90 units) in corn oil. C, April 4 (two weeks later) D, April 18 (two weeks later) E, April 21 (two weeks later) F, April 30 (two weeks later)

vitamin D in oil. However, in view of the fact that healing was not brought about in two of eight infants, this unitage in milk must be considered inadequate for curative purposes

From these experiences it would seem that milk which had been fortified with crystalline vitamin D resembled more closely milk produced from cows fed irradiated yeast rather than irradiated milk, in

asmuch as 45 units of crystalline vitamin D failed to cure all of the eight rachitic infants, whereas 90 units proved adequate

At first glance, it would seem that the increased effectiveness of crystalline vitamin D when incorporated in milk as compared with its administration in oil might be due to better absorption of vitamin D in the intestinal tract when the antirachitic factor is administered in milk. However, biologic assays of the feces of two infants who had been receiving 90 units of crystalline vitamin D in milk and of the

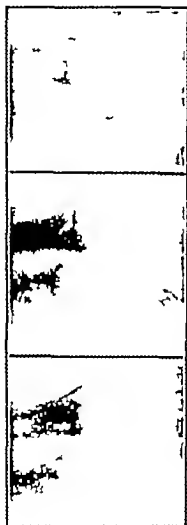


Fig. 7.—(T. R.) Absence of healing with crystalline vitamin D (50 units) in corn oil. A March 17 (begin) B April 19 (four and one-half weeks later) C May 1 (one and one-half weeks later)

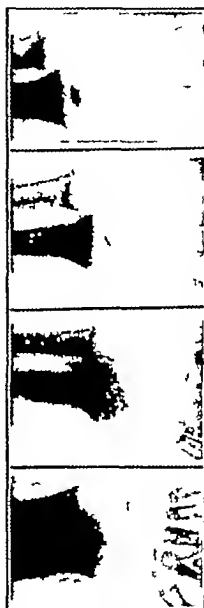


Fig. 8.—(R. R.) Absence of healing with crystalline vitamin D (90 units) in corn oil healing brought about by crystalline vitamin D (90 units) in milk. A February 16 (oil begun) B March 18 (milk begun) C April 1 (four weeks later) D April 20 (two weeks later)

feces of two infants who had been receiving 90 units of crystalline vitamin D in oil for the same period showed approximately the same amount of vitamin D. Samples of blood were also taken from these infants for assay of vitamin D in order to determine whether there was an increase of the antirachitic factor in the blood of those receiving crystalline vitamin D in milk. The results of this experiment revealed that there was no difference in the vitamin D content of the blood in both groups of infants. The superior utilization of crystalline vitamin D when administered in the menstruum of milk does not seem, therefore, to be due to better absorption of the antirachitic factor in the intestinal tract but a final decision concerning the role of absorption

TABLE I
COMPLEMENT IN THE CEREBROSPINAL FLUID

CASE	DIAGNOSIS	DILUTION OF CEREBROSPINAL FLUID						
		0	1 2	1 4	1 8	1 16	1 32	1 64
1	Meningococcus meningitis	0	0	0	0	0	0	0
2	Meningococcus meningitis	0	0	0	0	0	0	0
3	Meningococcus meningitis	+	0	0	0	0	0	0
4	Meningococcus meningitis	++++	++++	++	0	0	0	0
5	Meningococcus meningitis	++++	++	0	0	0	0	0
6	Meningococcus meningitis	0	0	0	0	0	0	0
7	Meningococcus meningitis	0	0	0	0	0	0	0
8	Meningococcus meningitis	++++	++	0	0	0	0	0
9	Meningococcus meningitis	0	0	0	0	0	0	0
10	Meningococcus meningitis	0	0	0	0	0	0	0
11	Meningococcus meningitis	0	0	0	0	0	0	0
12	Meningococcus meningitis	++++	+++	++++	++	+	0	0
13	Meningococcus meningitis	0	0	0	0	0	0	0
14	Aseptic meningitis	++++	+++	+	0	0	0	0
15	Aseptic meningitis	0	0	0	0	0	0	0
16	Aseptic meningitis	++++	+++	0	0	0	0	0
17	Pneumococcus meningitis	0	0	0	0	0	0	0
18	Pneumococcus meningitis	0	0	0	0	0	0	0
19	Pneumococcus meningitis	++++	+++	++	0	0	0	0
20	Pneumococcus meningitis	0	0	0	0	0	0	0
21	Tuberculous meningitis	++++	++++	++	0	0	0	0
22	Tuberculous meningitis	++++	++	0	0	0	0	0
23	Tuberculous meningitis	++	+	0	0	0	0	0
24	Hemolytic streptococcus meningitis	++++	++++	++++	++++	++++	++++	++++
25	Hemolytic streptococcus meningitis	++	0	0	0	0	0	0
26	Hemolytic streptococcus meningitis	++++	++++	++	+	0	0	0
27	Hemolytic streptococcus meningitis	++++	++	0	0	0	0	0
28	Hemolytic streptococcus meningitis	++++	++	0	0	0	0	0
29	Hemolytic streptococcus meningitis	++++	++++	++	0	0	0	0
30	Poliomyelitis	0	0	0	0	0	0	0
31	Poliomyelitis	0	0	0	0	0	0	0
32	Bulbar poliomyelitis	++	0	0	0	0	0	0
33	Poliomyelitis	0	0	0	0	0	0	0
34	Bulbar poliomyelitis	0	0	0	0	0	0	0
35	Influenzal meningitis	0	0	0	0	0	0	0
36	Influenzal meningitis	0	0	0	0	0	0	0
37	Influenzal meningitis	+++	+	0	0	0	0	0
38	Influenzal meningitis	0	0	0	0	0	0	0
39	Influenzal meningitis	0	0	0	0	0	0	0
40	Influenzal meningitis	0	0	0	0	0	0	0
41	Influenzal meningitis	0	0	0	0	0	0	0
42	Influenzal meningitis	++++	++	+	0	0	0	0
43	Influenzal meningitis	0	0	0	0	0	0	0
44	Influenzal meningitis	0	0	0	0	0	0	0
45	Influenzal meningitis	0	0	0	0	0	0	0
46	Influenzal meningitis	++++	++++	++	0	0	0	0
47	Influenzal meningitis	0	0	0	0	0	0	0
48	Influenzal meningitis	0	0	0	0	0	0	0
49	Influenzal meningitis	+++	0	0	0	0	0	0
50	Influenzal meningitis	0	0	0	0	0	0	0
51	Influenzal meningitis	0	0	0	0	0	0	0
52	Influenzal meningitis	++++	++++	++	+	0	0	0

TABLE I—CONT'D

CASE	DIAGNOSIS	DILUTION OF CEREBROSPINAL FLUID						
		0	1 2	1 4	1 8	1 16	1 32	1 64
53	Influenzal meningitis	0	0	0	0	0	0	0
54	Influenzal meningitis	0	0	0	0	0	0	0
55	Influenzal meningitis	0	0	0	0	0	0	0
56	Influenzal meningitis	0	0	0	0	0	0	0
57	Influenzal meningitis	0	0	0	0	0	0	0
58	Influenzal meningitis	0	0	0	0	0	0	0
59	Influenzal meningitis	0	0	0	0	0	0	0
60	Influenzal meningitis	0	0	0	0	0	0	0
61	Influenzal meningitis	0	0	0	0	0	0	0
62	Influenzal meningitis	0	0	0	0	0	0	0
63	Influenzal meningitis	0	0	0	0	0	0	0
64	Influenzal meningitis	0	0	0	0	0	0	0
65	Influenzal meningitis	0	0	0	0	0	0	0
66	Influenzal meningitis	0	0	0	0	0	0	0
67	Influenzal meningitis	0	0	0	0	0	0	0
68	Influenzal meningitis	0	0	0	0	0	0	0
69	Influenzal meningitis	0	0	0	0	0	0	0
70	Influenzal meningitis	0	0	0	0	0	0	0
71	Influenzal meningitis	0	0	0	0	0	0	0

+++ indicates complete hemolysis.

++ indicates seventy five per cent of cells hemolyzed

+ indicates fifty per cent of cells hemolyzed.

0 indicates twenty five per cent of cells hemolyzed

0 indicates no hemolysis.

dilutions in these tubes were 1 2, 1 4 1 8 1 16 1 32 and 1 64. Then 0.25 c.c. of a 5 per cent suspension of sensitized sheep cells was added to each tube. The tubes were shaken and incubated for one hour in the water bath at 37.5° C. Following incubation they were allowed to stand at room temperature an additional two hours to permit the unhemolyzed cells to be deposited to the bottom of the tubes. Readings of hemolysis were then made four plus indicating complete hemolysis two-plus indicating about 50 per cent hemolysis, etc.

One unit of complement would hemolyze 0.25 c.c. of sensitized cells* in these tests, according to the Hinton¹¹ technique for the Wassermann reaction. The results of these observations are recorded in Table I.

An analysis of these observations concerning the presence of hemolytic complement in the cerebrospinal fluid indicates that there is considerable variation in its presence. In most acute inflammatory conditions of the central nervous system it may be present in the cerebrospinal fluid in some cases. It is impossible to state just what factors are responsible for its appearance in some cases and not in others, even though the same etiologic agent may be operative. The degree of cellular response in the cerebrospinal fluid seems to bear no relationship to the presence of complement. In this series of cases complement was present more frequently in tuberculous meningitis than in the various types of purulent meningitis. The cellular response is of course much

All suspension of sensitized cell used in this study were very kindly provided by Dr. William A. Hinton's laboratory. The writer wishes to express his appreciation for this service.

less in tuberculous meningitis. Of great interest to us, at least, is the fact that complement was present much less frequently (in only five of thirty-six cases) in meningitis due to *B influenzae*. It is probable that those factors which may considerably alter the permeability of the meningeovascular barrier are responsible for the presence or absence of complement in the cerebrospinal fluid.

The hemolysis of sensitized cells which occurred in the cerebrospinal fluid of patients with hemolytic streptococcus meningitis is not necessarily due to complement. It is probably due, in most part, to streptococcus hemolysin in such spinal fluids.

DISCUSSION

The ultimate therapeutic value of complement in the treatment of meningitis still is an unsettled problem. Likewise, the exact mechanism whereby complement is operative in the serum destruction of those organisms causing meningitis is not entirely clear in all its details. It would seem most profitable to discuss these questions separately for meningococcus and *B influenzae* meningitis.

Meningococcus Meningitis

With regard to the biologic destruction of meningococci two immune mechanisms may operate: first, there may be simply a complemental bacteriolysis of the organisms; second, there may be a phagocytic ingestion and destruction of sensitized organisms with or without the activity of complement. It is quite probable that this latter mechanism is the more important.

Davis¹ showed that normal human serum was distinctly bactericidal for the meningococcus. This property was diminished but not entirely destroyed by heating the serum to 60° C for thirty minutes. Furthermore, meningococci were taken up by human leucocytes in the presence of human serum.

M'Kenzie and Martin² studied the bactericidal effect of human serums on meningococci. They found that the serum of normal individuals, patients with acute and chronic meningitis, and patients who had recovered had some bactericidal effect. It was much greater in patients who had recovered. The bacteriolytic action depended on a thermally stable immune body which required the presence of thermolabile complement to complete the process. These authors made no observations on phagocytosis.

Kolmer, Toyama, and Matsunami³ studied the opsonic activity of antimeningococcus serum in combination with normal serum. Normal serum or complement increased the opsonic activity of commercial antimeningococcus serum. For this reason these authors recommended the addition of 1 c.c. of fresh sterile human or guinea pig serum to each 9 c.c. of antimeningococcus serum.

In a subsequent paper Matsunami and Kolmer¹² found the bactericidal activity of horse antimeningococcus serum and normal human serum to be largely independent of complemental bacteriolysis. They found however, that the addition of normal serum definitely increased opsonic activity and again suggested its therapeutic use. Evans¹³ was unable to confirm the findings of Kolmer and his associates. She was unable to observe any reactivating effect when complement was added to commercial serum.

It is thus seen that the experimental evidence is incomplete regarding the role played by complement in the destruction of meningococci. Furthermore, practical therapeutic experience shows that many cases recover without the addition of complement to the antiserum. Indeed on the basis of the observations recorded in this paper, the majority of patients do not have complement in their cerebrospinal fluid yet the mortality has been reduced a great deal by serum therapy. We have had several patients who have made prompt recoveries in whom at no time during the course of the disease were we able to demonstrate complement in the cerebrospinal fluid.

On the other hand, an occasional patient, such as that of Bunim and Wics* may be distinctly benefited by the addition of complement to the immune serum. The evidence is certainly insufficient however to recommend this as a routine procedure in the treatment of meningococcus meningitis. Nevertheless if a patient fails to respond to a good specific serum and complement is absent from his cerebrospinal fluid it would appear to be worth while to supply it.

In this connection it should be remembered that the blood of most normal adult individuals frequently has a considerable meningococcidal power. This has been shown by McKenzie and Martin,² Matsunami and Kolmer,¹⁴ Matsunami¹⁵ and Heist S. Solis-Cohen and M. Solis-Cohen.¹⁶ Thus, human serum injected as complement may, in itself contain specific immune bodies for the meningococcus.

If complement is used in treatment, the amount used probably should be much greater than that recommended by Kolmer and his associates. There are two reasons for this view: in the first place a small amount of complement would be tremendously diluted by the relatively large volume of cerebrospinal fluid into which it is injected; second the Nelsson Wechsberg¹⁷ inhibiting phenomenon* undoubtedly would play a rôle. Thjøtta¹⁸ in his study of this phenomenon suggested that large amounts of complement may be necessary to overcome this inhibition.

In conclusion it would seem that the mechanism involved in the serum

It was observed by these authors that when antiserum and complement were mixed in a bacteriolytic system, there was no killing of organisms in the greater concentrations of antiserum. Killing occurred only when the concentration of antiserum was reduced markedly in relation to the amount of complement used. These observations which constitute this phenomenon have been abundantly repeated and confirmed.

destruction of meningococci should be restudied, particularly in respect to the newer knowledge of the antigenic structure^{19 20 21, 22 23, 24 25} of the meningococcus

B Influenzae Meningitis

The serum destruction of influenza bacilli has been studied particularly by Waid and Wright^{5 26} These authors have presented considerable experimental evidence that in the test tube the important killing mechanism is a complemental bacteriolysis, phagocytosis playing a very minor rôle In test tube bactericidal experiments the following results were observed

- A Inactivated immune serum plus organisms resulted in practically no bactericidal action
- B Inactivated immune serum plus organisms plus fresh normal serum resulted in good bactericidal action
- C Inactivated immune serum plus organisms plus washed defibrinated blood cells resulted in very little bactericidal action

In these experiments the Neisser-Wechsberg¹⁷ phenomenon was observed depending on the concentration of immune serum in relation to the amount of complement

These authors have also shown that in addition to complement the thermostable immune body must be capable of precipitating the specific soluble substance of virulent influenza bacilli in order to be effective Such an immune body results from a long period of immunization with a "smooth" or virulent antigen

Since the important killing mechanism, in test tube experiments, is complemental bacteriolysis and since complement is so rarely present in the cerebrospinal fluid of patients with *B influenzae* meningitis, the addition of complement to immune serum would appear to be definitely indicated in the therapy of this disease

CONCLUSIONS

It has been found that complement is present in the cerebrospinal fluid in a small minority of patients with various types of acute inflammatory disease of the central nervous system It is found only rarely in the cerebrospinal fluid of patients with *B influenzae* meningitis

A discussion of the use of complement in the serum therapy of meningitis is presented

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300 LONGWOOD AVENUE

GANGRENE OF THE FOOT FOLLOWING MEASLES

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ROCKY MOUNT, N C

GANGRENE, even including cancrum oris, following measles is rare. Morse¹ does not mention gangrene at all other than noma. Kerley² does not mention gangrene at all, even noma. Holt³ describes noma and says, "Gangrenous inflammations of other parts of the body are sometimes seen after measles, especially of the ear, the vulva, or the prepuce." Griffith,⁴ citing Leitz, says that thrombosis of the vessels may result in gangrene of the limbs in exceptional cases. Abt⁵ refers to the occasional occurrence of noma on other parts of the body, especially the genitals. Hoyne⁶ reports cases of scarlet fever, measles, mumps, chickenpox, and whooping cough, occurring in the same individual in a period of forty-six days followed by an acute symmetrical dry gangrene, which he diagnosed Raynaud's disease. Recently Dick et al reported a case of severe purpura with gangrene of the lower extremity following scarlet fever, and in June, 1934, the occurrence of massive skin gangrene complicating chickenpox was reported by Watson.⁸

On account of the dearth of information to be had from a perusal of standard pediatric textbooks and periodicals, one is forced to turn to treatises on dermatology for enlightenment concerning gangrene following the exanthemas. Schamberg⁹ mentions the rare occurrence of gangrene on various portions of the cutaneous surface, other than the cheeks and genitals, citing Thomas, of Paris, Mayr, Faye, Battersaye, and Carroll, who have seen such cases. Sutton¹⁰ states that dermatitis gangrenosa infantum, a rare disorder complicating varicella and vaccinia in certain cases, may more rarely follow measles and cites an instance reported by Thorp in *Lancet* in 1921. Andrews¹¹ published a photograph, by courtesy, of gangrene of the left knee and foot in that section of his text devoted to this condition. Whether this followed one of the exanthemas or developed independently was not mentioned.

CASE REPORT

Baby E. T., Jr., was fourth child of a tenant farmer who raised cotton and tobacco principally, some corn, and not enough hogs were raised to furnish the family with meat. He does not own a cow, the chickens are raised so haphazardly that there are no surplus eggs and chicken as a meat is not customary. The vegetable garden is merely a side issue and, because of the urgency of the call to the tobacco field, receives scant attention.

The baby, born normally at term, was breast fed with no regularity until after admission into the hospital. He had occasional attacks of colic as an infant, whooping cough which was said to be very severe at three months, and the mother says

that even now he loses his breath at times upon coughing. Since birth he has had constipation, for which the mother has been in the habit of giving castor oil. He sat alone at about the sixth month. Though he has had an occasional orange in his hand to eat of, he has not been given orange or tomato juice or cod liver oil. Since he was about six months old he has been given crackers or pieces of biscuit. For the past several months he has had fried meat skins and chicken bone to chew on. He has had some candy but no vegetables. The first dose of diphtheria toxoid was given five weeks before admission the other dose was not given because of the child's illness. He has not walked alone but before the attack of measles he could walk around a chair, using both legs equally well.

On January 28 the appearance of a rash, which proved to be measles, was noted. The mother said the rash had disappeared by the end of a week. Following this it was thought the child showed satisfactory improvement until February 10 when the child cried as if in pain. The parents were unable to discover any cause. The child appeared normally active and played throughout the next day but the mother discovered two ulcers on the right foot that evening when she undressed him for bed. When questioned, the mother said she had seen no sign of anything wrong with the foot prior to this time. The child was seen by his local physician and referred to Park View Hospital, where he was admitted Feb 13 1934.

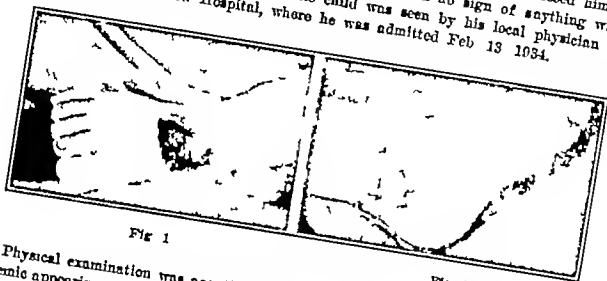


Fig 1

Fig 2.

Physical examination was negative except for the following. Patient was flabby anemic appearing white male infant with temperature 102 F. A slight nasal mucoid discharge was present, and there was some ulceration of the left nostril. The lymph glands of the anterior cervical chain were palpable. There was slight tenderness at the costochondral junctions and some flaring of the costal angles with Harrison's groove. Crepitant rales were heard posteriorly over both lungs. The abdomen was moderately distended and of the abdominal viscera only the spleen was palpable. The right foot was moderately swollen and presented two punched out ulcers. One on the dorsum extending in toward the inner malleolus, was roughly triangular in shape about 5 by 4 by 4 cm in size. The other roughly pentagonal in shape surrounded the outer malleolus and measured about 5 by 3½ cm. at the broadest diameter.

The laboratory findings were as follows. R.B.C., 4 810 000 hemoglobin, 55 per cent (Tallqvist) W.B.C., 24 000 polymorphonuclears, 30 per cent lymphocytes 70 per cent. A slight achromia was noticed blood Wassermann reaction was negative. The blood culture was negative up to six days urine examined at weekly intervals was negative except for an occasional pus cell.

For the first three days of his stay in the hospital, amertina was applied to the ulcers after that only dry sterile dressings were used. A frame was placed over the crib covered with sheets, and dry heat was furnished by electric light bulbs.

The ulcers appeared very painful for the first four or five days, requiring the administration of some Dover's powder. Cooked cereals were given twice daily. Vegetable soup or vegetable purées were given daily. The baby was weaned as quickly as possible. We met with considerable opposition from the mother on this point. However, the baby appeared to take lactic acid milk greedily. Mead's yeast, one teaspoonful in one half ounce of orange juice, was given every four hours. thirty drops of cod liver oil were given in each feeding (every four hours). Prunes were given twice daily. Beginning the second day of his stay in the hospital, ultraviolet ray treatments were given daily in gradually increasing dosage, just short of marked erythema. The ulcer sloughed, but we thought healing took place with remarkable rapidity. The temperature ranged above 101° F, the peak being 103.4° F, with short remissions until March 3. For about five days before discharge on March 14, it had ranged within one half degree of normal. The baby was taking food well and appeared to be generally quite improved when discharged from the hospital, although the ulcers had not completely healed over at that time. We have seen him three times since, the last time on Aug. 20, 1934, when photographs of the healed lesions were taken.

SUMMARY

1 An instance of gangrenous ulcerations of the foot following measles is reported.

2 From an analysis of the history one is forced to the conclusion that a nutritional deficiency existed. This probably predisposed the ulceration. "Measles may also aggravate a previously existing pathologic state, as tuberculosis, diabetes, heart disease, or other debility."¹²

3 On a balanced diet rich in vitamins and with the application of dry heat and ultraviolet ray, the child recovered satisfactorily.

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ACRODYNIA

ITS POSSIBLE CAUSE

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THE literature of acrodynia is so voluminous and the clinical descriptions of the disease so complete that we will not attempt to review them or comment upon them beyond stating that since the disease was first described arsenic has always been under suspicion as a causative factor, though it has never been shown to be the causative factor

The following case is reported, through the courtesy of Dr F L Day for three reasons first because we were able to discover the presence of a toxic agent in the patient, second because we were able to determine the source of that agent, and third for the purpose of stimulating investigation along the lines of our reasoning

CASE REPORT

F M., aged two years, male was admitted to the Bridgeport Hospital May 13, 1934, on the pediatric service of Dr F L Day Past history was negative. The child developed normally and had always been well fed

Family History—Father and mother were both living and well. One other child was living and well. There was no known exposure to tuberculosis.

History—The present illness began two months before admission when the patient had a severe attack of vomiting which lasted two days and was accompanied by some diarrhea. Within a short time he became irritable lost his appetite and gradually lost strength and weight. The bowels were inclined to be loose. An irritation developed on the buttocks and lower abdomen over the diaper area but no rash or discoloration of the skin was noted elsewhere.

These symptoms persisted for a month (April 16) when the child was admitted to another hospital. While there he ran a slight fever ranging from 100 to 101.5 F., developed a mild cough and had mucous rales in both lungs. It was noticed that he perspired profusely. X ray examination of the lungs and the Mantoux test were negative for tuberculosis. Stools examined for parasites were negative. The spinal fluid was normal. No skin findings were noted except on buttocks and lower abdomen.

The child was removed from the hospital after a stay of two weeks and a week later was admitted to this hospital.

Physical Examination.—The patient showed loss of weight and flabby musculature with sensitiveness of muscles on examination. He had no desire to stand or walk and was perspiring profusely. Some tremor of hands was noted. There was some irritability on examination, though not marked.

Head Hair was thick, not falling out. Eyes and ears were negative. Nose. There was no discharge, no redness of the skin. The throat was somewhat reddened with large ragged tonsils. The teeth were good. Mouth showed mild stomatitis.

In the lungs coarse, moist râles were heard over both sides. The heart was negative. The abdomen was scaphoid. No pain was elicited on pressure except in the muscles. The liver and spleen were apparently normal in size. No masses were felt. There was general redness over lower half of abdomen with marked papules irritated by scratching. Buttocks showed eruption of intertrigo type. Rectum was prolapsed about half an inch.

Extremities were clear except for distinct pinkish blush over all phalanges of fingers and toes and backs of hands and feet extending to wrists and ankles. Motion of these parts caused pain. Toes and fingers felt cold. There was marked itching of the hands, and especially of the feet. The child rubbed his feet together to relieve it. No desquamation was noted.

The day after admission one of us (C. V. C.) wrote: "Not acutely ill appearing, but pale and rather poorly nourished. Shows dry, pinkish, chronic looking, slightly scaling, fine papular eruption over entire abdomen and a considerable amount on back. Hands and feet are somewhat pinkish and look as though chronically irritated. Some of the finger nails look abnormal. Fingers and toes seem a little hypersensitive. Baby appears to have some nervous system disturbance, showing a little tendency to tremor and rather slow and prominent respiratory movements. Lungs show râles of varying size and type. Rather large, slightly congested tonsils. Otherwise not remarkable. Acrodynia. Tuberculosis?"

A few days after admission pustules appeared around the toe and finger nails and on the sides of the fingers and toes. These became ulcerated and desquamation began. After two weeks the child developed furuncles on the back, buttocks, and in the palm of the left hand, these cleared up without complications.

Convalescence was uneventful, except for an attack of chickenpox, and (September 1) the patient was apparently well. He still perspired freely, and there was some thickening of the skin of the hands. Otherwise he seemed quite normal.

Laboratory Findings—May 14. Hemoglobin, 93 (Sahli), R.B.C., 5,640,000, W.B.C., 7,250, polymorphonuclears, 49 per cent (Band 15), small lymphocytes, 39 per cent, mononuclear cells, 11 per cent, eosinophiles, 1 per cent. Blood appeared dehydrated.

May 15. Nose and throat cultures were negative for K. L. In the sputum smear acid fast bacilli were not found. Widal test. Serum (1:40) did not agglutinate either of two strains of *B. typhosus*, or *B. paratyphosus* A or B.

May 26. Wassermann and Kahn tests were negative.

June 12. Organism from abscess was *Staphylococcus aureus*.

June 22. Hemoglobin, 77 (Sahli), R.B.C., 5,040,000, W.B.C., 8,950, polymorphonuclears, 55 per cent (Band 11), small lymphocytes, 27 per cent, mononuclears, 15 per cent, eosinophiles, 2 per cent. Red cells were slightly small and hypochromic.

August 28. Hemoglobin, 83 (Sahli), R.B.C., 4,450,000, W.B.C., 10,600, polymorphonuclears, 47 per cent (Band 2), small lymphocytes, 37 per cent, mononuclears, 3 per cent, large lymphocytes, 8 per cent, eosinophiles, 4 per cent.

X-ray Examinations—May 14. A radiographic examination of the chest showed no evidence of infiltration in either peripheral lung field. Although the hilar shadows were moderately thickened, there was no evidence of calcification to suggest childhood pulmonary tuberculosis.

June 23. A radiographic examination of the bones of the knees, the forearms, and the wrists showed no evidence of gross pathology. There was a slight increase in the calcification at the distal diaphyseal ends of the shafts, especially in the wrists. There was no evidence of plumbism. The epiphyseal development appeared normal.

Having in mind the case reported by Meyer and Weise¹ in which arsenic in large amounts was discovered in the blood and urine, we investigated the diet to discover, if possible a source of arsenic. The most likely source seemed to be the home grown, home canned string beans which had been heavily sprayed with arsenate of lead by the patient's father and which had been a regular article of diet both fresh and canned. Accordingly, several cans of these beans, together with samples of the patient's hair, blood, and urine were forwarded to Dr C N Meyers to whom we are indebted for all of the analyses included in this report. These samples were collected twelve days after admission and showed the following amounts of lead and arsenic

Beans, sample 1—	0.84 mg	arsenic per 100 gm	of solid
Beans, sample 2—	0.083 mg	arsenic per 100 gm.	of solid
Beans, sample 3—	0.29 mg	arsenic per 100 gm.	of solid
Bean juice—	0.259 mg	arsenic per 100 gm.	of solid
Hair—	0.078 mg	arsenic per 100 gm	of solid
Urine—	0.24 mg	arsenic per 100 gm.	of solid

Beans, sample 1—	4.3 mg	lead per 100 gm.	of solid
Juice, sample 1—	9.5 mg	lead per 100 gm.	of solid
Juice, sample 2—	10.4 mg	lead per 100 gm.	of solid

Unfortunately the amount of blood submitted was insufficient

These figures are high. The amount of arsenic in the hair is greater than that found in the hair of a person who was suffering from the symptoms of arsenic poisoning,² and the same is true of the amount found in the urine.³

On the other hand a sample of urine collected twelve weeks after admission showed 0.059 mg arsenic per 100 gm of solid and 0.026 mg of lead per liter. A sample of blood collected at the same time showed a trace of arsenic and of lead 0.98 mg per 100 gm of solid (normal 0.05 mg).

Three theories are most commonly advanced as to the cause of acrodynia: first, that the condition is an infectious one; second, that it is an avitaminosis; and third that it is due to dysfunction of the vegetative nervous system. To these we would like to add a fourth or perhaps amend the third—that is, that acrodynia is the result of metallic poisoning acting on the vegetative nervous system in peculiarly susceptible individuals. In our opinion the metals causing this poisoning may be arsenic and lead in combination such as is found in the widely used insecticide *arsenate of lead*.

Some of our reasons for this theory are as follows:

Before the use of insecticides this disease was unknown. With the increase in their use the disease has become more prevalent.

The results of treatment point to the fact that the disease is due to the ingestion of some toxic material. Various treatments have been advocated, ranging all the way from removal of the tonsils to special diets. They all seem to have been successful. They all have one thing

in common. That one thing is a change in diet. In almost every instance this change in diet has been brought about by removing the patient to a hospital.

Considered from this point of view much evidence in the case reports is corroborative. In reporting a group fed with liver, the author³ says of one case, "This case is interesting because an attempt was made to give the liver treatment at home—the treatment had apparently completely failed—and the child was admitted to the hospital for further trial," with success. Here the diet was certainly changed by removing the patient to a hospital and apparently no improvement was noted until the change in diet.

In a series reported by another author⁴ we read, "The patient was admitted in September, 1929, and after eleven weeks was discharged (at the parents' request) improved, was readmitted in January, and died four weeks later." Here the diet was changed with resulting improvement which was undone, in our opinion, by a return to the original toxic diet.

That lead arsenate may be the toxic article in the diet is indicated in other reports. One writer⁵ has it that "three weeks before admission the child ate a large quantity of canned cherries and had a severe attack of diarrhea." Analyses have shown the possibilities of arsenic and lead in this particular kind of canned fruit.² Again we read⁴ of a child who "dwelt in poor circumstances on a farm, though the mother gave the child good care and nourishing food" (Our own patient dwelt on a farm, and his mother gave him good care and nourishing food. His diet was entirely adequate and well balanced.) Of another case the author states that "during the two months previous to admission the mother had difficulty in feeding the baby, who was accustomed to cow's milk and vegetable broths." Both of these cases strongly suggest arsenate of lead in the diet. Our own case showed it.

Apparently the length of time during which the toxic agent is ingested before a change in diet is made has a great deal to do with the ultimate outcome of the disease. A recent report⁶ of an autopsied case states that the patient had been ill for approximately six months before admission to the hospital, during which time he had been treated at home. In another series⁴ a case terminated fatally, which "began eleven months previous to admission" and another fatal case in the same series "showed evidence of long-standing illness." On the other hand, patients who had had symptoms for "eight weeks," "two months," "nine weeks," "four weeks," and "three months" previous to admission all recovered.

The autopsy findings in the nervous system are not at all incompatible with what we would expect to find in chronic lead poisoning. The similarity of the disease to chronic arsenic poisoning was noticed

long ago We feel that this symptom complex may very well be due to the action of arsenic and lead *in combination*

In the case presented we know we had arsenic poisoning We know we had lead poisoning as well But the clinical picture was that of acrodynia

Is acrodynia arsenoplumbism in peculiarly susceptible individuals?

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144 GOLDEN HILL STREET

881 LAFAYETTE STREET

AN IMPROVED CONTAINER FOR HYPODERMIC SYRINGE

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THE administration of a hypodermic injection in the doctor's office is a simple procedure. In the patient's home it is often a cumbersome and time-consuming operation because of the lack of adequate facilities for sterilizing syringes and needles. Yet in spite of the obvious disadvantages incident to boiling a syringe in a kitchen pot over the stove, most physicians prefer this to carrying a previously sterilized syringe in an inadequate container, particularly one which cannot itself be boiled. Such cases must be filled with some type of disinfectant fluid, none of which is as certain in its antiseptic action as boiling, and many of which may have a deleterious effect upon injectable biologic products.

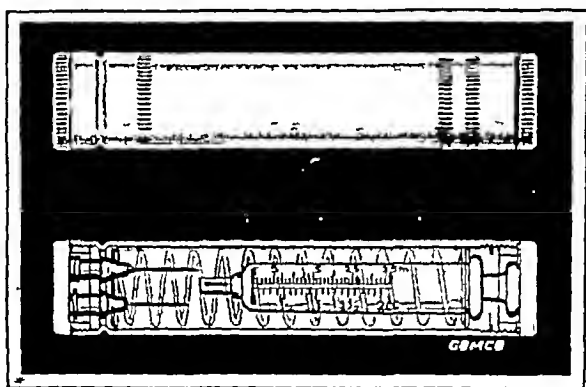


Fig 1

As a solution to this problem a case has been designed which will carry a dry syringe and maintain its sterility under all conditions. It is made entirely of rust-proof metal and is unbreakable. It will hold firmly a 2 c c syringe of any design and two hypodermic needles of any style or length. The syringe, needles, and case may be boiled together, and, when the two caps are then screwed in place, the contents are unquestionably and permanently sterile. The caps are water-tight and air-tight, and therefore, no matter how carelessly the case may be knocked about in the doctor's bag or what liquid may be spilled upon it, there is no possibility of contamination.

The outfit is made shockproof by means of pressure from a flexible coiled spring which prevents the contents from rattling about and thus

insures against dulling of the needle points and breakage. The same spring causes the syringe to protrude slightly when the cap is removed thus facilitating its easy extraction from the case.

Because the case is impervious to chemical action of all liquid sterilizing mediums, these may be used when indicated (as for example by a diabetic patient on a journey during which several injections of insulin must be taken with no opportunity to boil the outfit between injections). An important feature of this set is the fact that sterilization may be attained by boiling the entire outfit, including the case. The absence of a blind bottom allows free circulation of the boiling water and promotes cleanliness. After boiling, the syringe need not be touched and no fluid need be added.*

*This case is manufactured by The Gomco Surgical Manufacturing Corporation, Buffalo, N. Y.

Critical Review

GROWTH AND DEVELOPMENT

THE ENDOCRINE GLANDS AND GROWTH

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WINNETKA, ILL

THIS series of reviews on the subject of growth and development is attempting to present the subject first, from the standpoint of the nature of growth as a process and second, from that of the various physiologic and biologic factors acting upon the process. It has been shown that general growth occurs in a series of waves, or curves superimposed upon a more gradual increment in the development of each individual and that in the various separate organs and tissues in the body, differing growth rates prevail so that the summation is an orderly development in which nutritional and functional demands are met as they arise in the normal individual. The stimuli which give rise to these growth rates, both general and in specific tissues, are little understood, but some of the factors, such as the vitamins and hormones, are gradually emerging into the light of day. For the unknown factors we have to fall back upon such indefinite terms as organismic pattern or natural tendency.

It has been shown quite clearly that most of the vitamins exert a marked effect on general growth since deprivation of any one of them, except possibly vitamin E, results in complete cessation of growth. In addition to this influence upon the general growth impulse, all of them exert effects of specific nature on separate organs or tissues of the body as, that of vitamin A on epithelial structures, that of vitamin B on nervous tissues, that of vitamin C on the vascular system, etc. In this present consideration of the endocrine glands and their secretions as they affect growth, the situation is somewhat different. With the brilliant exception of the growth hormone of the anterior pituitary gland, their effects upon general growth are much less conspicuous, and their results upon specific structures are, if anything, more sharply defined.

It must be understood clearly that both vitamins and hormones probably act as specific catalyzers of general and local growth, influencing living protoplasm which is unfolding according to some underlying, less obvious control.

Our understanding of the respective rôles of the various endocrine glands in the general and specific growth problems is made more difficult by another factor not complicating our consideration of the vitamins. This is the fact that the various glands with their multiple hormones comprise a system interacting upon themselves to a degree and in a manner of which we are only partly aware. This has been and probably will continue to be a source of error in the appraisal of

the effects of separate hormones. However it will probably be best to consider the glands separately realizing that they seldom act as independent units.

Another fact seldom mentioned in the consideration of the relation of hormones to growth is the reactivity of the receptor tissues to these substances. Smith and Engle bring out the point that hormone effects depend upon the sum of endocrine stimulating power and the ability of the tissues to respond. Thus it has long been known that in making limb and organ transplants in amphibia and other lower animals the ultimate size of the transplant is dependent upon the size of the donor rather than upon that of the recipient. No amount of endocrine stimulation has enabled investigators to enlarge transplanted tissues beyond the size of the species from which they originated. A differential growth rate is therefore present which is to a certain extent independent of hormones.

THE PITUITARY GLAND

Because the pituitary, or hypophysis elaborates the general growth hormone and because we are beginning at least to understand some of the interrelationships between this gland and other endocrine structures it affords a logical starting place in this discussion.

Historical

The hypophysis has been known to exist since the time of Galen A.D. 200 when its function was supposed to be that of lubricating the throat. This idea held until about 1660 at which time it was overthrown by Schneider who considered the gland a vestigial structure. About 200 years later, in 1864 we see the first implication in the literature that the pituitary is of importance in growth. Verger reported the case of an acromegalic giant with an abnormal pituitary gland. Again thirty years later Klebs published a monograph on acromegaly and demonstrated abnormally large pituitary glands in his cases. Marie in 1886 definitely established a relationship between this gland and acromegaly but considered the disease due to a deficiency. In 1871 Lorraine described pituitary dwarfs. Before this in 1840, Mohr had reported a patient suffering from the condition we now recognize as pituitary adiposity with hypophyseal tumor revealed at autopsy. But it was not until 1901 that Fröhlich described the syndrome which now bears his name dystrophia adiposogenitalis. In 1895 Oliver and Schafer discovered a secretion recovered from the posterior lobe which was effective in raising the blood pressure. Cushing in 1912 published a monograph on pituitary tumors and their effects as well as his results in surgical treatment.

It was not until after 1920, however that the isolation of the separate hormones took place. Evans described the growth hormone in 1921. Smith the ovulating sex stimulating hormone in 1926 and Zondek the luteinizing hormone in 1928.

The foregoing brief sketch of the history of research in this subject omits the names of many who have contributed much to our knowledge and is not intended to be complete. Engelbach in his work *Endocrine Medicine*, gives a detailed account for those historically inclined.

ANATOMY AND HISTOLOGY

It is necessary, before one can understand the pituitary function, to have clearly in mind the anatomy and histology of the gland, as well as its relationship to the neighboring brain. The organ is found in all vertebrates. Its origin can be noted in the human embryo as early as the fourth week, at which time the upward extending pouch from the oral cavity has made contact with the infundibulum descending from the brain. The epithelial portion, that from below, forms the anterior lobe, the neural portion gives rise to the posterior lobe. Between these two is the cleft, and along the cleft margin of the posterior lobe lies a thin envelope of epithelial tissue which develops into the pars intermedia. Along the infundibular stalk lies a similar sheet of cells forming the pars tuberalis.

It would at once seem likely, because of its twofold origin, epithelial and nervous, that the gland would not function as a simple secretory organ. One immediately thinks of the similarity between this arrangement and that found in the suprarenals with the glandular cortex and the medulla so intimately associated with the sympathetic nervous system. The products of the anterior lobe, with which we are here chiefly concerned, are probably taken up by its rich vascular supply and distributed to the body by this route. Those of the pars intermedia and pars tuberalis, however, are probably not disseminated in this manner because the blood supply is very poor and because the anatomic relationships indicate that they are either discharged into the brain cavity, or are stored in the posterior lobe and adjacent brain substance, and are slowly given up from these structures. Hoskins says "Determination of the function of the pituitary as such is rendered difficult by uncertainty as to the precise relationships between the gland and the adjoining parts of the brain. Injuries of this region of the brain, hypothalamus, produced experimentally, by accident, or by the growth of tumors, have been shown to lead to such disturbances as obesity, excessive urine formation, and abnormalities of sugar metabolism. Very similar disorders are producible experimentally by injuries to the pituitary. There is some evidence, also, that from the brain tissue in the hypothalamic region can be obtained an active extract that shares in the properties of pituitary derivatives. A third paradoxical element in the situation is that severe injuries of the hypothalamic region may either produce the abnormalities just mentioned or may result in no detectable disturbance of function whatever. The answer to the riddle at this time can only be surmised. The known facts suggest that the pituitary and the hypothalamus stand in an intimate relationship somewhat similar to that of the adrenals and the sympathetic nervous system. It would appear to be true that the composite mechanism normally acts as a unit susceptible of disturbance in either of its parts with ultimately similar results, but that either the nervous or the glandular mechanism can substitute for the other. As specific evidence in favor of this latter supposition, the fact can be cited that profuse urinary output caused by injury to the hypothalamus can be readily controlled by administering an extract from the posterior lobe."

Since recent advances in our knowledge have enabled us to tell the exact hormones elaborated by some of the cell types, the histology of the hypophysis has become of primary importance. In the anterior

lohe there are three predominant types of cells, first, the alpha, acidophilic or eosinophilic cells, known to secrete the growth hormone second, the beta or basophilic cells which probably secrete the sex-stimulating hormones and third, the chromophobe, reserve or chief cells, whose function is not finally established. These are all polygonal cells with granules and are named after the staining propensities of these granules. Some authors believe that the chromophobes are the parent cells of the other types, others that the chromophobes secrete the sex hormones, though this is doubtful. In the adult gland the eosinophilic cells comprise about 37 per cent, the basophilic about 11 per cent, and the chromophobes about 52 per cent of the cells. These relationships are not constant throughout life, however much interesting work is being reported upon this subject.

In addition to these three types seen in normal glands under two pathologic conditions other types are seen, pregnancy and castration cells. The cells of pregnancy occur in such large numbers as to cause gross enlargement of the gland at this time. After delivery they decrease but do not entirely disappear. The cells of castration appear after this operation together with an increase in the percentage of eosinophiles. This checks nicely with the well known increase in stature of eunuchs operated upon before closure of the epiphyses. Castration cells are two or three times the size of the alpha and beta cells, and the protoplasm, which contains granules, stains pink.

The cells of the central portion of the posterior lobe are neuroglial except for a few epithelial cells which appear to have migrated from the pars intermedia. Since the blood supply of this structure is so poor it is not considered that it has a secretory function. The fact that potent extracts may be prepared from it, however indicates that it has a storage function for the hormones elaborated by the neighboring pars intermedia and pars tuberalis.

The pars intermedia, which also has a poor blood supply, is distinguished histologically by (1) cells resembling the chromophobes (2) elongated cells which may be stained by the Golgi method, and (3) cysts containing colloid and hyaline material. It is thought that the cells of the pars intermedia secrete the posterior lobe extract which is merely stored in the pars nervosa before absorption into the circulation or brain cavity. It is also supposed that these cells secrete the hormones that dilate the melanophores of frogs and other animals.

In the pars tuberalis no granular cells are found but the cells are arranged in columns about cavities with no epithelial lining. These cavities are not found until the fifth postnatal month. Squamous cells are also found extending out into the pars nervosa, to the floor of the fourth ventricle, and into its nervous tissue.

In the infantile period the two portions of the gland are not united entirely, and the intervening cleft is distended with colloid material. The anterior lobe is filled with small, pale appearing cells. Chromophobes are present in the first year. During the juvenile period there is marked increase in the size and number of the eosinophiles and development of the pars intermedia. At adolescence there is a marked increase in the basophiles and chromophobes which persists until the age of about forty. At this time there are relatively fewer eosinophiles, and the cleft progressively closes. In old age the cleft is com-

pletely closed uniting the gland into a compact mass. The epithelial cells diminish, connective tissue increases, and the gland becomes less vascular.

It is known that the hypophysis functions during fetal life because potent extracts have been made from pig embryos of half full size and because its removal notably in tadpoles has prevented subsequent normal development of structures known to be under pituitary control, thyroid and supra-renal glands.

This histologic résumé is given because it shows that the appearance of the gland cells under the microscope coincides roughly with the functional demands of different age periods. During the major growth epoch the acidophilic cells reach their greatest development, and during sexual maturation the basophiles reach their maximum percentage.

THE EXPERIMENTAL APPROACH

It is interesting to note the steps by which our knowledge of hypophyseal function has progressed. At first, on the basis of proximity alone, it was assumed that the gland secreted a fluid into the throat. When this hypothesis, after centuries, was overthrown the gland was thought to be merely vestigial. Then, as a result of careful autopsies, various observers established its relation to growth disorders: first to acromegaly, then to dwarfism, dystrophia adiposogenitalis, and gigantism. At about this time, when it became apparent that a gland of internal secretion was being dealt with, attention was shifted from the growth aspects of the problem by the discovery of the posterior lobe hormones which had no growth function.

It was not until the era of experiment upon lower animals that the growth factor again became of major importance. The effects of pituitary removal, destruction, transplantation, and feeding were studied in hundreds of experiments. These were at first crude and inconclusive because of surgical difficulties encountered and because of the fact that true pituitary effects were difficult to evaluate in animals with intact hypophyses. The ideal experiment was to remove the glands from animals, note the effects, and then to attempt replacement therapy with feeding, transplantation, or hormone injection. This line of investigation was given great impetus by a perfection of technique by Smith, who showed that in the rat complete removal trans-orally was possible without disturbing the brain. This obviated the secondary results known to follow injury to the hypothalamic region. Since this technique was discovered, evidence as to the exact influence of pituitary secretion on growth has rested upon unusually firm experimental ground. The growth- and sex-stimulating hormones have not only been demonstrated, but they have also been isolated.

Along with this experimental activity in the laboratories resulting in hundreds of articles and books, great interest has been displayed in the clinics explaining the pathogenesis of pituitary disturbances on the basis of endocrinologic advance and pointing out new hypophyseal syndromes such as basophilic adenoma, Cushing's disease, and pituitary cachexia, Simmond's disease. At the present time, since this topic is in its most active phase, one expects to find pituitary disclosures in almost any medical periodical. Whether we are on the verge of discoveries which will make us masters over general growth through

the growth hormone or give us control of maturation processes through the sex hormones is a matter for the near future to decide

For many years a controversy raged as to whether or not pituitary hormones were necessary for the preservation of life. This issue was complicated by imperfections in the technique of operative removal and lack of sufficient long time mortality statistics on the animals. According to Evans it is now quite evident that removal of the hypophysis has no immediate serious effect upon life. He is equally sure however that 'most hypophysectomized animals succumb from cachexia before anything like a normal life span has been passed.'

THE GROWTH HORMONE

The isolation of this specific hormone was largely due to the work of Evans and his collaborators. It is known to be secreted by the acidophilic cells of the anterior lobe. As far as can be established, the growth hormone stimulates growth in every structure in the body. When the pituitary gland is removed from immature animals, the effect is immediately noticed in cessation of growth and development. As a corollary growth can be reestablished in these same animals by administration of the growth hormone or by pituitary transplantation.

There seems to be no clear cut statement of opinion in the material which has come to my attention as to the mechanism of this growth stimulation. However Collip and his coworkers have this to say

— a few facts which we believe are important in the understanding of the mechanism of the action of the growth hormone. We have observed that the compensatory hypertrophy of the remaining kidney occurs in hypophysectomized rats after unilateral nephrectomy; furthermore Dr Jeffers has found in his laboratory that mitotic figures are plentiful in the mammary glands of hypophysectomized rats at the time of parturition. It is also well known that the proliferation of epithelial cells and fibroblasts in wound healing is not seriously interfered with by hypophysectomy and that transplanted tumors grow, though not as rapidly as usual, in hypophysectomized rats. All of these observations show that the proliferation of cells and the growth of the individual organs are not necessarily dependent upon the growth hormone. That animals may survive hypophysectomy for several years shows distinctly that cells of the various organs that died during this period have been replaced by new ones. The present paper shows that even a general growth though not increase in length of the osseous system may be produced in the absence of the pituitary growth hormone.

'We conclude that the growth of the various organs in themselves is largely independent of the hypophysis. Apparently the function of the pituitary growth hormone is only to permit enlargement of the size of the body as a whole with a harmonious and proportional increase in the size of all the organs.'

It would be interesting to learn what effect, if any, this hormone would have on tissue cultures. It seems to me that the statement quoted above might imply that maintenance cell division could proceed without the growth hormone but that general growth and development under specific organismic patterns is stimulated by this substance.

While removal of the hormone causes a cessation of growth and a condition of status quo, Evans remarks that "this is not the establishment of a perpetual youth, for the capacity of the body in many measurable ways has been injured." In dwarfs, for instance, he states that there is actual shrinkage of the epiphyseal cartilages and gradual obliteration by dentin of the pulp cavities of the incisors, together with marked disturbance of the calcium metabolism and reduction of the blood calcium. This last may possibly be due to secondary parathyroid insufficiency. The failure of the bones to increase in length is apparently due to lack of the formation of cartilage in the epiphyseal discs.

Not only has the growth hormone restored growth in hypophysectomized animals, but also gigantism has been experimentally produced. These growth effects have been most perfectly attained with the preparation of Evans. Reichert warns that the sex-stimulating hormones must be completely removed in such solutions because they tend to close the epiphyses and stop growth. It is noted that there is a decided sexual difference in response to this hormone, the males reacting less promptly to administration and withdrawal of the hormone.

Most laboratories use rats in the test for the presence of the growth hormone because in this and similar species the epiphyses remain open during adult life. As a result, it is possible to measure the stimulus to body growth after maturity. In practice, the test applied is to use animals between five and nine months old which have reached a stage of development called the "growth plateau," in which their slight weekly increment is known by previous observations. Intraperitoneal administration of potent extracts will produce marked accelerations.

In experimental animals the growth of which is being stimulated by the hormone, more protein is stored and less consumed than normally. This effect is comparable to that of insulin in the sugar metabolism.

In answer to the question as to the purity of the preparations produced, Evans states: "It is easy to produce a white hygroscopic powder, stable for months at room temperature in dry, air-exhausted chambers and capable of producing maximum results in adult female rats in doses of considerably less than 0.5 mg. daily. The powders have almost 15 per cent of nitrogen, all in the form of protein or a protein-like body, and it is difficult to break this down further without losing efficiency. It appears that just as they are proving helpful in the isolation of enzymes, selective absorption methods will be of great importance here."

In the earliest stages of development, growth seems to proceed without the activation of this hormone. In amphibia the pituitary has been removed before structural differentiation was demonstrable in the gland. Such larvae develop to the tadpole stage at a rate only slightly retarded, after which they show the effects of hormone deficiency unless administration is artificially afforded. Secondary failure of the thyroid to develop is a contributory cause for this lack of development for partial compensation is seen when the thyroid hormone is given such animals.

Considerable skeletal growth takes place in the rat when the pituitary is removed even as late as the weaning period. Later in life, however, growth is immediately stopped by hypophysectomy. Difficulties in technique have prevented investigators from discovering whether or not removal of the gland at birth would stop growth, but

from the observation above it is thought that some growth would take place under these conditions. This is one of the reasons why most investigators doubt that congenital growth disturbances such as achondroplasia are due to endocrine factors.

One of the most interesting pituitary growth anomalies I have seen referred to is noted by Smith and Engle that of hereditary dwarfism in a strain of mice. In this strain, dwarfism occurs in the mendelian ratio, and the dwarfs are sterile. In the offspring of the heterozygous apparently normal animals, growth proceeds as usual for about fifteen days, after which it may rather abruptly slow down and finally stop entirely. The pituitary glands of these dwarfs are undersized and histologically show complete absence of acidophilic cells.

THE GONADOTROPIC HORMONES

Although these hormones do not directly influence general growth they produce marked effects on specific growth of the organs concerned with reproduction. There are two and possibly three, such hormones that which stimulates the ovulation function one which increases luteinization and possibly one which fortifies the pregnancy urine hormone. Understanding of the gonad stimulating hormones is complicated by the fact that the sex glands themselves secrete hormones and by the fact that additional endocrine products in pregnancy and castrate urine have gonadotropic effects. For these reasons it is necessary to define these various substances and give their sources as far as is known.

The female sex hormones are estrin and progesterin, both secreted in the ovary. The first functions in promoting estrus and in the development of the secondary sex characteristics, the second in the processes of pregnancy, luteinization etc. Their production is stimulated by the pituitary gonadotropic hormones, and in turn the sex gland hormones inhibit the production of those from the pituitary.

The pregnancy urine hormone, prolactin or theelin causes stimulation of the corpora lutea and probably originates in the placenta, according to Smith. It is often spoken of as a pituitary hormone an error partly due to the different nomenclatures used in various countries. In male animals this substance stimulates the secretion of the interstitial cells of the testes and consequently hastens development of secondary sex characteristics. Engle and others have used it to promote descent of the testes in cryptorchidism. Of course it is not of interest in the male from a physiologic standpoint because males are not under normal conditions exposed to its effects.

The castrate urine hormone, on the other hand acts upon the follicles of the ovary in females and upon the tubules of the male according to Smith. It is considered by many authors that this is a true pituitary hormone, but absolute proof is lacking.

It is established beyond doubt that in all young experimental animals, as well as in human beings, removal of or destruction of the pituitary results in lack of development of the sexual system. In mature animals the same lesions cause regression of the system. Sex interest is lacking in such animals. The germ cells, ova and sperms, however remain alive in the tissues, and subsequent administration of pituitary hormones is capable of complete restoration of sex function. In young rats the stimulating effects of pituitary transplants on the

sexual system are evident almost immediately, in two or three days, the females responding more rapidly than the males. This sexual hypertrophy or premature development, however, is anatomic rather than physiologic because functional maturity does not occur until the adolescent age in the various species.

Evans devotes considerable space to a discussion of a fraction of the pituitary secretion which interacts with prolactin to form the most potent sex-stimulating substance known. He and other authors consider that these two substances activate each other because neither one alone is as potent as are the two combined. Of the two, the pituitary fraction is by far the most potent. This prolactin-stimulating substance is different from the two well-known gonadotropic hormones of the pituitary. Separate preparation of the gonad-stimulating hormones is being attempted but has not been accomplished.

Since the true sex gland hormones inhibit the production of those from the hypophysis, several investigators have referred to their interaction as the cause for the female sex rhythm. To quote Hoskins, "when the pituitary activity is at its height, it is assumed that this leads to the induction of a new sex cycle. The augmented supply of gonad hormones then leads to the unfolding of the sequential development in the sex organs and at the same time induces a quiescent period in the pituitary. The sex hormones having waned the pituitary resumes activity and a new cycle is begun. Such observations quite justify the designation recently conferred upon the anterior pituitary, 'the motor of the gonads'."

THE LACTOGENIC HORMONE

Work by Riddle and Corner and others makes it seem probable that the anterior pituitary secretes a hormone capable of stimulating mammary glands. This hormone, prolactin, is apparently potent only on mammary glands prepared by the sex hormones. Under its influence virgins and even male animals have been made to produce milk. This hormone may be of great importance to pediatricists if it is prepared in a form practicable for use in human beings. The writer feels, however, that even with a potent lactagogue in our hands there would still be plenty of mothers who would not be able to nurse their babies.

THE THYROTROPIC HORMONE

Evidence as to the existence of this hormone rests upon the established fact that removal of the pituitary gland results in reduction in the size of the thyroid gland and in changes in the epithelium which lead to the formation of squamous cells with flattened nuclei. The substance has not yet been isolated in pure form.

Hypophysectomy results in a lower basal metabolic rate than that produced by thyroidectomy. This is probably due to the fact that hypophysectomy also affects the suprarenal glands, which exert an influence on basal metabolism. In experimental animals exophthalmos has been produced by administration of the pituitary thyroid-stimulating substance. This is explained on the basis of superstimulation of the thyroid.

THE ADRENALOTROPIC HORMONE

When the hypophysis is completely removed from experimental animals, in addition to the changes previously mentioned, there is an almost complete atrophy of the adrenal cortex. It has been thought

that the gradual decline in vigor and health that the animals showed might be due to the lack of cortin. On the other hand in such animals, whereas the administration of cortin did not improve their condition aqueous alkaline extracts of the anterior pituitary caused an immediate favorable response. The substance in the anterior pituitary responsible for this change is apparently closely allied to the growth hormone not to the gonadotropic fraction. It has been assumed that under normal physiologic conditions this pituitary secretion activated cortin. It may be that in the future a pituitary hormone may be used either alone or in conjunction with cortin in the treatment of Addison's disease.

THE PARATHYROID-STIMULATING HORMONE

Evidence suggests that there is a pituitary substance which stimulates parathyroid activity, but this is as yet inconclusive.

THE PITUITARY AND OBESITY

Since operative techniques which did not disturb the neighboring brain have been used adiposity as a result of hypophysectomy has become a rare observation. Pituitary dwarfism produced under the best modern techniques is not associated with adiposity. Consequently the concept that the syndrome of Fröhlich was due to lack of pituitary hormones has been losing ground. It is being more and more generally thought that this is a disturbance on a nervous basis due to hypothalamic dysfunction.

On the other hand, Anselmino and Hoffman have isolated a substance from the anterior lobe which when injected into animals increases the acetone bodies in the blood. Under normal conditions this substance is found in the blood only when fat is being burned and would seem to tie the pituitary with fat metabolism. That Cushing's disease, pituitary basophilism is characterized by adiposity of the face, neck, and trunk, raises the question as to whether the hypophysis can be disregarded in this connection. It is, of course, conceded that pituitary tumors cause adiposity by pressure effects on contiguous areas in the brain. Probably the central and autonomic nervous systems are quite as potent factors in adiposity as are the hormones.

THE DIABETICOGENIC HORMONE

Since this hypothetical hormone has no direct effect on growth and development it is mentioned for the sake of completeness only. It is likely that diabetes of pituitary origin is a clinical entity.

THE RELATIONSHIPS OF THE GROWTH AND GONADOTROPIC HORMONES

It is apparent from the results of animal experimentation and also from a few clinical facts that the growth and sex hormones of the hypophysis are mutually inhibitory. When the sex hormones are included in the material injected into rats to produce growth for instance much less increment is obtained than is the case when the growth hormone is given alone. Also it is a well known fact that in acromegaly a disease due primarily to increased production of the growth hormone marked decrease or absence of sex activity is noted.

It is interesting that in this small gland there are lodged the determiners of youth and maturity. As long as the activity of the acid

ophilic cells and the consequent production of the growth hormone predominates, general growth and particularly that of the epiphyses proceeds. But with the increase in function of the basophilic and chromophobic cells in the pituitary and the resulting rise in production of gonadotropic hormones, maturation takes place rapidly, and with this process the epiphyses close and growth ceases. This cessation of growth is absolute in higher animals but may persist in much modified degree in some lower forms such as the rodents.

Not only are the pituitary gonadotropic hormones antagonistic to growth, but also the true sex hormones elaborated in the sex glands share in this property. This probably accounts for the phenomenon of eunuchoid gigantism. In the absence of sex hormone inhibition the growth hormone continues its influence on the organism, producing great stature.

THE POSTERIOR LOBE HORMONES

So far, the secretions of the anterior lobe only have been discussed. It is almost certain that the pars nervosa has no secretory function although, as is well known, extremely potent hormones may be extracted from this tissue. It is more probable that the hormones that cause increased smooth muscular contraction and decrease the urinary output are elaborated by the pars intermedialis and pars tuberalis and excreted into the pars nervosa and around the infundibular stalk into the brain cavity, thus accounting for the hormone activity of extracts from this region. It is possible that a fat metabolic agent may also be elaborated and secreted in this manner.

Since none of these hormones are directly concerned with the growth problem, it is proper to dismiss this subject with this brief statement rather than to discuss the voluminous arguments and evidence.

CLINICAL IMPLICATIONS FOR THE PEDIATRIST

Any structure so vitally influencing growth must be of absorbing interest to physicians limiting their work to patients in the growing period. Just how far we are justified in assuming that laboratory results obtained on lower animals, or even on primates, are applicable to human beings is an open question. While we certainly cannot apply all of them at face value, some of the facts seem so uniformly true in all species that it is justifiable to assume, until the contrary is proved, that they apply to human beings.

Dwarfism of the pituitary type, in which there is no bodily disproportion, may command our close attention from the standpoint of therapy in the near future. Such dwarfs vary greatly in their appearance and functional capacity according to the time of onset and the severity of the pituitary deficiency. They vary also depending on whether the growth function alone, or that plus the gonadotropic function is impaired, resulting in such individuals in many states of physical and sexual development. Their mentality is not, as a rule, affected except so far as their psychic make-up is changed by the fact that they are more or less freaks to the rest of mankind. In addition to the infantile proportions, receding chin, flat chest, protruberant abdomen, low umbilicus, and delicate skin, it is found that the epiphyses do not close. Some of these men and women have lived to very old age and were quite famous characters in history. If they mature sexually, they may propagate and their children usually grow to normal stature.

Engelbach has reported the successful administration of the growth hormone to such a patient, a nine-year old girl. Von Monakow produced rapid growth in a fourteen year-old dwarf with the same substance, and other cases in which the use of this hormone has been effective have recently been reported. As far as I know the growth hormone is not as yet available commercially, but when it is, its availability will present many perplexing problems to the practicing pediatricist. We will have to decide upon proper indications for its use and answer such questions as 'what is a dwarf?' The reviewer feels that the responsibility added to the profession would be so great that this biologic substance should be given thorough trial in established clinics before it is marketed to the profession at large. Perhaps I am over-timorous but I shrink from the thought that in my declining years I might have to face resentful patients protesting that I had made them too tall or had neglected to make them tall enough.

Pituitary gigantism is a clinical entity resulting from overproduction of the acidophilic cells before the age of puberty, in reality a juvenile acromegaly. The overgrowth of the body is more uniform than in acromegaly, however because the epiphyses have not yet closed. Sexual function, as might be expected from what we know, is usually decreased.

It is conceivable that this disease might prove amenable to treatment with gonadotropic hormones which tend to close the epiphyses and bring on maturity. Since excessive stature is, in my opinion, a much more tragic situation than being undersized, this subject may well interest the clinician of the future.

Pituitary cachexia, Simmond's disease has received considerable attention from practitioners treating adults. Silver in his report cites no instance of this condition in a child. However I have recently had under my care a fourteen year-old girl who presented this syndrome. She lost 40 pounds in one year, stopped menstruating, showed a basal metabolic rate of minus 30, microsplanchnia, lassitude, and anorexia. After obtaining an increase of symptoms if anything with thyroid administration, she immediately improved when given antinutrin subcutaneously, 2 c.c. daily. For a week she gained 1.5 pounds daily and finally has put on 34 pounds. All of her subjective symptoms have disappeared but to date menstruation has not been reestablished. It would not be surprising to find that some of the more obscure maladies characterized by growth disturbance have their basis in pituitary dysfunction. Premature senility, progeria, bears a marked resemblance to pituitary cachexia.

In all cases of *thyroid* and *adrenal dysfunction* the pituitary factor must be considered because of the marked stimulating effect which the hypophyseal secretions exert upon these glands.

Since *pituitary basophilism*, Cushing's disease, and *acromegaly* occur only in adults, they interest the pediatricist only as they illustrate the multiple effects produced by overactivity of two of the cell types in the anterior hypophysis, the basophiles and the acidophiles, respectively.

Pituitary basophilism is characterized by obesity confined to the head, neck and trunk, decreased sexual activity, hirsutism, cyanosis, polycythemia and decrease in the calcium of the bone and in the blood sugar. This disease has always proved fatal in a few years. The symptoms are explained on the basis of basophilic adenoma with over

production of the gonadotropic hormones, pressure effects, and secondary endocrine abnormalities due to the influence of the pituitary on other ductless glands

Acromegaly is usually due to adenomatous overgrowth of the acidophilic cells. It results in growth of all parts of the body still capable of responding to the growth hormone. Enlargement is noted in the acral parts, in the periosteum, tongue, skin, nasal cartilages, larynx, and in the hair growth. In women it is customary to state that they become more masculine, exhibiting virulism, an effect presumably due to secondary adrenal stimulation. As is the case in basophilism, pressure effects may cause complications in the picture due to dysfunction of the posterior lobe and of the hypothalamic region of the brain.

Pubertas praecox of pituitary origin and *pituitary eunuchoidism* and *myxedema* have been described but are extremely rare clinical conditions.

It is probable that *dystrophia adiposogenitalis*, Frohlich's syndrome, and allied conditions will be much better understood as soon as experimental work on the relation of the hypophysis to fat metabolism clarifies the atmosphere. We have all seen so many of these fat, hyposexed children develop into tall, sexually competent individuals without therapy that great care must be used in evaluating reports.

As far as the value of oral administration of pituitary hormones is concerned, there is much difference of opinion. Research workers almost unanimously contend that gland extracts are impotent when given by this route. Yet, many competent clinicians have reported results which seemed favorable. This is one of the many controversial issues which will have to be decided by experience. In the meantime it behooves us to keep an open mind.

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Round Table Conference on Infantile Eczema

Leader Dr Lewis Webb Hill, Boston Assistant Dr Irvine McQuarrie Minneapolis

CHAIRMAN HILL—Urbach says in his book, *Skin Diseases and Nutrition*, "Whoever seriously tries to deduce from such a mass of controversial opinions and contrasting personal experiences, any definite conclusions as to the proper treatment of infantile eczema surely finds himself in a quandary."

He is right for two reasons. First, under the heading "infantile eczema" are grouped a number of different dermatoses. Furthermore individual skins may react to the same stimulus with different types of eruption or to different stimuli with the same type of eruption. Second there is no disease in which it is easier to make false observations or to draw incorrect conclusions from true observations—much very unsound material has appeared in the literature.

In spite of the fact that there are included under the heading "eczema" several different conditions, it is probably best for our purposes to include them under one heading for they are so closely interrelated and one may shade into the other so imperceptibly that it is often not possible to make clean-cut and sharp distinctions until we know a good deal more than we do now.

For the present we may include under the heading "the infantile eczema group" the following conditions:

- 1 Seborrheic dermatitis
 - A. Erythrodermia desquamativa
- 2 Allergic eczema
 - A. Atopic eczema
 - (1) Infantile
 - (2) Chronic in older children
 - B. Contact dermatitis
- 3 Mivotic eczema

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is characterized by patches of inflammation with scaling. The scales may or may not be yellow and greasy. There is no vesiculation, and there-

This of course should not be called "eczema," but it is so often clinically indistinguishable from chronic eczema and so many times is superimposed upon an atopic eczema that it is probably best to include it in the group.

fore no oozing. It begins usually on the scalp, extending to the forehead and cheeks, or may occur in patches on the body. As regards infants, we may perhaps recognize two varieties: the first corresponding exactly to the adult type, with rather sharply margined patches on the face, chest, or back and the usual scaling. This is not very common. The second, or more common, type, seen especially in young infants, is characterized by greasy scales on the scalp, or "cradle cap," and some involvement of the cheeks and forehead, but not in sharply defined patches. I am not at all sure that we should call this seborrheic dermatitis, but there is certainly plenty of seborrhea of the scalp and dermatitis of the face. This may clear up, or it may develop into a true eczema as the baby grows older, with vesiculation and oozing and wider distribution. It may be often looked upon as the first stage of eczema. Seborrheic dermatitis in its pure form is not an allergic disease, but, on the other hand, since a great many allergic infants with eczema have seborrhea of the scalp, it may be said that in young infants it is often impossible to draw a hard and sharp line.

The dermatologists themselves do not know accurately the etiology of seborrheic dermatitis. From time to time various observers have isolated special fungi and have claimed that it was a fungus disease. Some recent work is by McLeod and Dowling in England,* who isolated a fungus that they call "pityrosporon," and reproduced lesions similar to seborrheic dermatitis, by inoculation with it. This has not been generally accepted by dermatologists, however. The fact that clean cut, typical cases of the disease are usually cured with sulphur and salicylic acid does indicate its possible parasitic origin, however. In infants, particularly, it is probable that metabolic errors play an important part, but the nature of these is unknown.

As a subgroup under seborrheic dermatitis, we should include that curious and little understood condition, erythrodermia desquamativa, which begins in the first few months of life and is characterized by an intense redness all over the body, usually with a good deal of scaling and always with well marked seborrhea of the scalp. It is looked upon by Moro as the "hohen typus" of seborrheic dermatitis, because in the milder forms with a patchy, instead of a diffuse, redness they are very similar. In some cases there may be almost no scaling, simply an intense redness all over the body, it may be that these several forms are in reality different diseases, but it seems best for the present to include them in the same group. In the pure form of this condition there is not the vesiculation of true eczema, but I have seen cases of atopic eczema with positive skin tests, which cases were very similar to erythrodermia. It is very likely that an allergic baby with an added marked seborrheic tendency may react with the picture of erythrodermia rather than with the usual scattered vesicular eruption of atopic eczema. In its typical form it is probably not allergic.

No one knows anything about its etiology. The most varied, and sometimes the most fantastic, methods of treatment have been recommended, but here again it is apparent that but little of real value is known. I have had very good results in some cases with a low fat and sugar and high casein diet. In the cases in which this diet has worked, I have seen the skin clear entirely in from three to six weeks. It is important to pay a good deal of attention to the nutrition of these babies, not to underfeed them, and to start a full mixed diet as soon as possible. They cannot be cured by any local treatment, and boric acid ointment or vaseline with salicylic acid does as well as anything.

ALLERGIC ECZEMA

For the ¹	of ecz ²	gy may be defined as a condition of hypersens ³
tiveness t	to w ¹	id individuals are not sensitive
*Brit	n 130	" 1930

Under the heading "allergic eczema" I would include atopic eczema and contact dermatitis. Atopic eczema is often hereditary may be associated with asthma or hay fever, and gives positive skin tests to proteins by the scratch or intracutaneous method also reagins in the blood can often be demonstrated by passive transfer

A baby two or three months old begins to have seborrhea of the scalp and an eruption on the cheeks, which soon becomes vesicular and oozy and spreads to the outer sides of the lower legs or to any part of the body. In the beginning in very young infants skin tests to proteins may be negative (shown so well by Smyth) but as the baby grows older the tests become positive particularly to egg.

This is a very important and interesting baby because, since he represents the very first stages of allergy, it is always instructive to study any disease condition in its primitive form. He may have eczema for a while and recover from it spontaneously he may be cured by intelligent treatment he may develop chronic eczema with multiple sensitivity and have it for years or he may develop hay fever or asthma with or without the eczema and be an atopic individual the rest of his life.

About two-thirds of all cases of eczema in infants and children are atopic. Skin tests to proteins are of very considerable value in dealing with this group. As you all know there has been a great deal of discussion as to whether the cutaneous or intracutaneous test is more valuable. More recently the passive transfer test has come into the field. It has seemed to me that the cutaneous test is the best, for many reasons, in dealing with infants and children. If the same concentration of atopen is used there is no question that the intracutaneous test is more delicate but in cutaneous testing a very concentrated solution is ordinarily applied and if done properly it should very closely parallel testing by the intracutaneous method.

In very sensitive infants generalized reactions are not uncommon with the intracutaneous test and I was told in New York recently that in the last year there had been three fatalities there as a result of this test. The method of passive transfer may be used occasionally if an infant's skin is covered with eruption too much for scratch tests, but is not very practical for general use and applies more to certain special cases or to investigative work than it does to routine work in the clinic or office.

For infants the most common allergens giving reactions are egg wheat and milk. In older children sensitivity to foods tends to lessen, and sensitivity to epidermals takes its place notably cat hair.

Skin tests have been found positive by various observers in from 40 per cent to 80 per cent of different series of cases of eczema. In my own series the incidence is about 60 per cent. If one carefully selects those cases which appear clinically to be of the atopic type that is, the 'true eczema' of Moro, the incidence is higher. He obtained 80 per cent positive reactions to egg white in this group.

The frequency of egg reactions is most interesting probably very important and not entirely clear. In my own series, egg reactions occurred in about 55 per cent, and in forty-six infants under six months of age who gave positive tests to something forty-two reacted to egg and twenty-four to egg alone in spite of the fact that they had never eaten egg. In a similar series of forty-six the ages between six and twelve months only 12 reacted to egg alone, and in another series between the ages of two and twelve years only eight. It may be taken as a fact based upon some very accurate work by Moro in Heidelberg and Wöringer in Strasbourg that these egg reactions are due not to some nonspecific irritating quality of egg white but to a true and specific egg sensitivity. It is evident that these eczematous babies who are egg sensitive and who are not eating egg are not having eczema from the egg and that egg sensitivity in many cases should be looked upon as an index of allergy rather than as an immediate cause of the symptoms. The origin of this

tion is of the epidermis rather than of the cutis, and sensitivity is tested for by means of the patch test by which a small amount of the suspected substance is applied to the unbroken skin and covered with adhesive tape. The reaction is a delayed one, and usually appears in forty eight hours or more. The reaction is not urticarial but is manifested by small vesicles on an erythematous base, and sometimes the sensitivity is so exquisite that severe dermatitis is started by the test. In the acute forms the character and distribution of the eruption usually serve to distinguish it from atopic eczema, in the more chronic forms the two may be very hard to differentiate. Chronic atopic eczema, however, has a predilection for the front of the elbows and back of the knees, contact dermatitis occurs anywhere, but especially on exposed surfaces, such as the face, hands, or forearms. In contact dermatitis there is almost always some tendency to vesiculation, in chronic atopic eczema there rarely is. This conception of eczema and the use of the patch tests were brought to America by the pupils of Bloch and Jadassohn and have been of the greatest possible value in dermatology, more particularly for adults.

In children, if the eczematous process began during the first few months of life, it is almost surely atopic, if it began suddenly on a previously healthy skin at some time during later childhood, it may be of the contact variety. Since very little work has been done with contact dermatitis in babies and children, I do not feel at all certain how common it may be. The infant and young child come into relatively little contact with the things which cause this type of eruption, and it is probably not nearly as important in infants and children as in adults. I have recently seen, however, three cases in young children which were apparently contact dermatitis, two probably from the dye in clothes and one from turpentine.

I have not been able to duplicate Dr. Peck's work with patch tests. In a series of twenty five cases, using the same technique and the same allergens,* I have had no positive reactions whatever. If this paper is carefully studied, it will be seen that most of his positive patch tests were to feathers. In a group of twenty five consecutive infants in my clinic with the usual type of facial eczema, I found that fifteen slept on no pillow, four on kapok or cotton pillows, and only five on feather pillows. Practically all of Dr. Peck's babies slept on feather pillows. Furthermore, I have had recently a number of cases with very strongly positive scratch tests to inhalants, cattle hair, silk, cottonseed, and cat hair, and patch tests in these cases gave no reaction whatever. I should, however, like to see a large series with negative scratch tests, tested by the patch method with the same nonprotein substances that are used for adults. The subject of contact dermatitis in infants and young children is practically an unexplored field and needs much further study. The distinction between contact dermatitis and atopic eczema is an important one, and it seems likely that while the so called "external" protein allergens (cat hair, silk, and cottonseed) may occasionally work by contact, they more often work by inhalation.

MYCOTIC "ECZEMA"

In the last few years fungi have assumed great importance in dermatology, and many eruptions hitherto classed as eczema in adults have been found to be in reality fungus infestations. The two organisms responsible for most of these eruptions are members of the trichophyton group and *Monilia albicans*, the organism of thrush. There are many reports in the literature of yeastlike fungi (cryptococci) having been found in various eczema like dermatoses, but these forms occur so often on normal skin that their etiologic significance is in some doubt. *Monilia albicans* does not apparently occur on normal skin and if this is recovered, the chances are that it is the cause of the skin lesions.

*Dr. Peck used the same allergens in protein powder form that are ordinarily used for scratch or intracutaneous tests in atopy.

Little has been done as regards the presence of these infestations in infantile eczema. Schamberg in 1915 reported one of the first cases of thrush of the skin in an infant and Peck has reported a case of trichophyton infestation in a child of fifteen months, but there is practically no information as to how common these infestations may be in what is ordinarily called 'eczema.'

In the last two years I have been very much interested in this question and have been using the intracutaneous monilia and trichophyton tests routinely. It is too early to make any very definite statements or to be sure of the value of these tests, but so far the work seems to indicate the following:

1 Trichophyton infestation is very uncommon in infants and children and is of little or no importance as a cause of 'eczema.'

2 Monilia (thrush) infestation may be of some importance either as a primary cause or as a contributing cause of 'eczema' in from 10 per cent to 15 per cent of all cases as it occurs in young children.

3 Monilia is probably of no importance in the ordinary facial type of infantile eczema. But if there are patches of scaly eruption in the groins, or large rather sharply defined areas on the body, or involvement of the fingers and nails, we should suspect the presence of this infestation.

Knowledge of infantile eczema is by no means adequate, but with the invaluable help of the dermatologists and allergists the subject has certainly become much less obscure than it was a few years ago. We should follow closely their work with adults and take unto ourselves as much of it as seems applicable to our own particular field.

A few procedures in the therapy of infantile eczema really may work a great many which are often used can do no good whatever. If we can learn what is useless and prevent ourselves from doing things that are not founded upon sound observation and carefully interpreted facts, we shall have gained a good deal.

DR. IRVINE McQUARRIE—Dr. Hill's comprehensive review of the subject makes a foundation for any new approach to the subject because he has presented the problem in such a way that we all must have entirely open minds about it. Approximately two years ago Hansen conceived the idea of investigating the possible clinical bearing of a discovery made in 1929 by Dr. George Burr and his wife regarding the requirement in animal nutrition for unsaturated fatty acids. These workers, and almost simultaneously Mendel and his colleagues, discovered that rats placed on completely fat free diets which were adequate in all other respects soon developed a definite syndrome characterized in the early stages by scalliness of the skin and in the later stages by cessation of growth, necrosis of the tail and pathologic alterations in the kidneys. Burr found that when he added certain fats to the diet of these experimental animals they again began to grow and the skin scalliness disappeared entirely. He later found that the essential substances were the unsaturated fatty acids in the fat such as linoleic, linoleic and possibly urachidonic acid which have double bonds in their molecules.

Hansen empirically began feeding linseed oil to certain eczematous babies receiving no other form of therapy. After a period of a few weeks he found that several babies whom he was treating by this method in the out patient department were very much better. Since patients with eczema are not so common, he could not investigate this observation as fast as he wished. Therefore, he obtained samples of blood from rats fed on fat free diets in Dr. Burr's laboratory and on these determined the total iodine absorption values of the serum and the iodine number of the serum fatty acids as he had previously done in the case of normal and eczematous infants. He found in a short time that he was getting very low values in the experimental rats just as he had in the eczematous infants.

New eczema patients have been taken into the hospital where he could make careful clinical observations and at intervals determine the iodine number of the serum fatty acids in duplicate. To date over thirty of the patients studied in this manner have been found to have lower iodine absorption values during the active phase of the disease than normal control subjects of similar ages.

A large majority of these patients have shown marked improvement with no treatment other than feeding them linseed or corn oil, that is, products high in unsaturated fatty acids and restraining the limbs to prevent scratching. Accompanying this clinical improvement Hansen has found the iodine absorption value of the serum to increase from subnormal to essentially normal levels.

In a few cases he has tried the effect of tar ointment, a standard form of local treatment which is recognized as being very effective in clearing up the skin lesions temporarily. These patients as well as those subjected to the oil treatment were kept on the regular ward diets. He found that these patients, when successfully treated with tar, showed a similar increase in the serum unsaturated fatty acids.

These observations do not tell, of course, whether this phenomenon that Hansen has observed is the result of the eczema or whether it is an underlying basic factor in the etiology. Certainly we have continued to look, as Dr. Hill pointed out, for general constitutional systemic factors rather than just local factors, that is, for some reason why these babies have eczema where the normals do not. I think that the factor of allergy has satisfied most people, but I can see that it does not satisfy Dr. Hill, nor does it seem to me to meet all of the requirements of a satisfactory theory because I have had similar unsatisfactory experiences with patients. We get patients who have skin sensitivity and who do not improve after withdrawing from the diet the material to which they are skin sensitive. Again we see babies responding well to withdrawal of other substances to which they are not skin sensitive. While allergy is a constitutional factor that one can hardly escape, there may well be others of equal importance, such as the dietary factor that I have discussed here.

It is rather interesting that von Groer, of Vienna, in the course of studies on the relative nutritive values of carbohydrate and fat kept two babies for periods of several months on fat free diets. It was noted incidentally that one of the babies developed what he called an "exudative diathesis" at the end of three months. The author comments about this in a semihumorous way to the effect that this observation was rather odd in the light of Czerny's claim that fat intolerance is an etiologic factor in infantile eczema. It appears that what he actually did was to deprive these patients of unsaturated fatty acids for one thing. The effects of fat free diets have not been reported by other observers, as far as I know. One of our colleagues volunteered last winter to go on a fat free diet and has remained on it for approximately six months now. I have examined him semiweekly for any change whatsoever that might result, but clinically he has remained entirely normal. His iodine number has fallen from 122 to 95. Whether, after he has been on it for another few months, he will develop skin eruptions or not cannot be predicted. I doubt whether he will show anything, he feels perfectly well and is getting along satisfactorily. That does not prove anything as regards the growing infant, of course. We know that an adult kept indoors on a diet free of vitamin D does not develop rickets of the infantile type. Osteoporosis finally develops, but not typical rickets. Thus, our adult subject may not develop eczema under conditions favoring its development in an infant.

As regards the mechanism of local treatment with tar ointment, we cannot speculate too much, but it is interesting to note the fact recorded by Hendel and Malet, of Montevideo, that application of tar ointment to the skin of mice produced an increase in the neutral fat of the liver and certain changes in the skin lipids. This discovery points to a generalized or constitutional effect. These results, together

with the observation that application of tar ointment to one eczematous area of skin is often followed by improvement of areas not treated, indicate that there is a constitutional effect from local application. Some have argued that coal tar has no specific effect at all because control areas of skin, to which it is not applied, often improve as well as those treated, but one can interpret it just as well the other way.

I would like to say in conclusion, regarding this preliminary work on the relationship of fatty acid metabolism to infantile eczema, that no rigid claim is made for it as a final word regarding etiology or as a panacea for all eczematoid lesions. The observation is simply recorded that there is a disturbance in the unsaturated fatty acids of the blood plasma in many cases. I think you will agree with me that it is a rather promising lead for approaching the problem from a new angle. Undoubtedly as this is tried all over the country with inadequate doses of oil, we are going to have some discordant results. There will be overenthusiasm in some quarters and discouragement in others as with all new procedures but I believe that some genuine advance toward solution of the eczema problem is in the offing in this direction.

DISCUSSION

DR. JOHN RUHRAH (BALTIMORE, Md.)—I would like to ask Dr. McQuarrie how much oil he gave, was it taken and tolerated well, and whether olive oil would be borne better? Did the infants get entirely well?

DR. McQUARRIE—We cannot say what the optimal dosage is yet, but usually it is in the neighborhood of an ounce a day—all the way from half an ounce to two ounces a day in babies ranging from five to eighteen months. Sometimes part of the fat in the milk is removed and the oil whipped with the milk, at other times it is fed with cod liver oil.

The effect, clinically, is fairly striking. There was no recurrence within a period of about twelve days. The baby went home clear and came back erupted again. There may be some external factor but his iodine number had gone down from about 111 to 85. Whether the eczema had produced the low iodine number or whether the fact that he had discontinued the oil some time previous to leaving the hospital and had had no more, I don't know. Dr. Hansen has had other patients who have gone five months without showing any recurrence. He has had some who have been free from eczema for considerably over a year.

CHAIRMAN HILL.—Did you use a purified linseed oil?

DR. McQUARRIE.—It is raw linseed to avoid lead, as occurs in the process of 'boiling.'

CHAIRMAN HILL.—Have you ever used that special artists' oil that is pure white?

DR. McQUARRIE.—Dr. Hansen has used raw linseed oil obtained for this special purpose by our hospital drug department.

CHAIRMAN HILL.—Is the corn oil fairly efficient if you give enough of it?

DR. McQUARRIE.—Yes, if edible oils are probably all less effective than the linseed oil, the effectiveness apparently being directly dependent upon the content of linolic acid. The iodine number which measures the degree of unsaturation of the fatty acids, runs from 20 to 30 in ordinary cow's milk fat and from 40 to 60 in breast milk. That of linseed oil varies between 160 and 200. Other oils show intermediate values.

their eczematous babies, securing normal controls at the same time, we shall learn more about it than we ever can by working haphazardly. Patients like one little boy who is in our hospital at the present time with an eczematoid eruption may not respond to oil administration, but they differ from those who do in having normal serum fatty acid iodine numbers. Infection ought also to be noted. We had in the hospital for several months an eczematous patient with otitis media and infection around her ears and in the cervical glands with a relatively low serum iodine number in spite of nearly two ounces of linseed oil a day. Following the disappearance of the infection, the skin gradually cleared, and the iodine number of the serum fatty acids returned to normal.

CHAIRMAN HILL—Infection can work in two ways, it is very common to see a baby with very severe eczema get some sort of infection with a high fever and have his eczema disappear overnight. We have all seen that, and then, when he gets rid of his infection and fever, the eczema comes back the same as before. Not infrequently during acute upper respiratory infections a baby or young child will have hives, and it is also true that if there is a chronic focus of infection anywhere in a child with eczema, it is a very good plan to clear it up. I don't believe that infection accounts for the underlying process in most cases.

DR McQUARRIE—Hansen uses the Page, Pasternoch and Burt modification of the Rosenmund Kuhnherin method for his iodine number determination. It is quite an easy technique for chemists who do that work in the laboratory.

DR FRED RITTINGER (CLEVELAND)—Have you ever used soy bean oil?

DR McQUARRIE—Not since this study has begun. Sobee, which Dr Hill introduced, contains nearly all the fat as olive oil.

DR RITTINGER—What is the iodine number of soy bean oil?

DR McQUARRIE—I do not know.

DR WARD E COLLINS (KALAMAZOO, MICH)—Have you seen children with eczema for a long time who fail to grow and gain and who seem to be suffering from an infection with considerable glandular enlargement and fever?

CHAIRMAN HILL—Yes, I think that applies particularly to chronic cases in children from a year to three years old with general glandular enlargement, very red skins, they are pretty miserable children all around. There is some underlying process going on which we don't understand.

DR BARBA.—Rotner found that, if the mother was inoculated with horse serum late in pregnancy, a passive transfer developed in the individual offspring a varying period after birth which transfer was lost as the child grew older.

CHAIRMAN HILL—That is much what happens in atopic eczema. The child is born normal and doesn't begin to have eczema until he is three or four months old. He is eating nothing but milk but is apparently sensitive only to egg.

Has anyone any suggestions or ideas to offer as to the local treatment of eczema? Or have any of you had any experience with hyponallergic milk?

For some time in every case of milk sensitivity which gives good reactions to casein, or lactalbumin, I have been testing also with goat's milk and human milk, with milk heated to 130° C with casein amyloids, a digestion product of casein, and milk peptone, a digestion product not broken down as far. Almost all patients who give reactions to cow's milk will react to goat's milk, and most patients who react to casein will react to the heated milk as strongly as they do to unheated milk. If I have a case of real milk sensitivity, I very much prefer

a milk free diet rather than trying to get around it in any other way. Although if there is only a lactalbumin sensitivity evaporated milk is often indicated and I like to use it as a routine feeding anyhow for many cases. It is very easily digestible.

I don't use sobee a great deal except in milk-sensitive cases sometimes for very bad cases, not of milk sensitivity, it does well. As regards various milk formulas—shifting around from one type to another does not make enough difference to amount to anything.

DR. DONALD C. MEBANE (Toledo, Ohio)—I continually underfeed the infants a little and give them variety in order to prevent infantile eczema.

CHAIRMAN HILL.—Overfeeding is a very potent cause of eczema.

I think we get better results with crude coal tar locally than with any other one thing. But it is black and dirty. Within the last few months we have used a white tar, different from any of the other white tar preparations, which may amount to something.

DR. E. G. PADFIELD (Salina, Kan.)—I would like to ask Dr. McQuarrie if using the crude coal tar locally raises the iodine number any appreciable degree?

DR. McQUARRIE.—In the few observations made so far the iodine number has been low to begin with and after the patients had been treated with crude coal tar preparations and the eczema had cleared up the iodine number had increased. Whether it is the tar or whether there is some indirect factor that raises it as the patient gets better I could not say.

DR. PADFIELD.—In the light of your work, my treatment of these patients seems terrible. I had been firmly convinced that fat probably caused more harm in the eczematous children than proteins, consequently I have put them on a fat free diet and used coal tar ointment with apparently good results.

DR. McQUARRIE.—It may be that the coal tar is doing that.

CHAIRMAN HILL.—Perhaps I can answer that to a certain extent. The first idea of the harmful effects of fat in eczema was brought out by Czerny with his 'exudative thesis'. If a baby is grossly overfed with fat, taking away some of the fat will do him good but nowadays with whole milk mixtures instead of cream mixtures, no baby is grossly overfed with fat. The effect is not directly on the eczema, but on the nutrition of the skin. The type and intensity of eruption is dependent upon the nutrition and chemistry of the skin. Some babies will show one type of eruption and some another type, for that particular reason.

In certain fat babies who have probably a good deal of fat in the skin and the seborrheic type of eczema with fatty, greasy scales, getting rid of some of the fat in the diet will do them good. Getting rid of the fat in the usual baby who is too overnourished, does not do a great deal of good.

DR. A. B. GROSSMAN (Cleveland)—Do you find that by taking children away from their homes, especially the poorer homes and hospitalizing them, their eczemas, especially of the infectious type, clear up without any treatment, just by altering the hygienic care?

CHAIRMAN HILL.—Positively I am sure of that. The question of taking eczematous babies into the hospital is not easy to decide. They pick up infections quickly and are very likely to die. We have had some very unfortunate experiences with several eczematous babies in hospitals. Dr. Schwartz has written a good deal about it, as you know.

PEDIATRIC SERVICE IN GENERAL HOSPITALS

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES OF THE AMERICAN ACADEMY OF PEDIATRICS (CONTINUED)

THE second report concerns hospitals in Region II of the American Academy of Pediatrics. Only hospitals having at least twenty four beds for children are considered. Bassinets are included in the pediatric service when that service is under the direction of a pediatrician.

Region II represents the states of Alabama, Florida, Georgia, Kentucky, Louisiana, North Carolina, Oklahoma, South Carolina, Mississippi, Tennessee, Texas, Virginia, and West Virginia. In this entire region there are only twenty one hospitals having an infants' and children's service of twenty four or more beds and bassinets.

The following Table I gives the distribution of the respective services by states and the relative sizes of these services.

In twelve states and among twenty one hospitals, all of the services combined have a total bed capacity of 1,162, bassinets, 601. The largest number of beds in any one hospital is 215, the smallest, 18. The largest number of bassinets is 75, the smallest, 12. Two hospitals do not include bassinets in their report and apparently do not have them. In no state are there more than three 24 bed services. Kentucky and Tennessee each have three. All others have only one or two.

Residents—Ten of these twenty one hospitals employ a full time pediatric resident. One employs two residents. All pay the resident a salary which varies from \$25 to \$80 per month. In four instances the pediatric resident does not serve exclusively in the pediatric department.

TABLE I

STATE	NO OF HOSP	TOTAL BEDS	TOTAL BASSINETS	LARGEST NO OF BEDS IN 1 HOSP	SMALLEST NO OF BEDS IN 1 HOSP	LARGEST NO OF BASSINETS IN 1 HOSP	SMALLEST NO OF BASSINETS IN 1 HOSP
Ala.	2	87	63	48	39	40	23
Fla.	2	54	58	30	18	40	18
Ga.	1	38	--	38	38	--	--
Ky.	3	150	127	90	30	75	26
La.	1	143	69	143	143	69	69
N C	2	88	74	56	32	50	24
Okla.	1	215	17	215	215	17	17
S C	1	50	--	50	50	--	--
Tenn.	3	115	62	56	29	30	12
Texas	2	115	54	80	35	30	24
Va.	1	32	55	32	32	22	22
W Va.	2	75	55	40	35	30	25
Total	21	1162	601				

Internes—Four hospitals offer a special internship in pediatrics. Sixteen offer rotating internships in which part of the time is spent exclusively in pediatrics. The usual period of the latter service is one, one and one half, or two months.

Attending Staff—Eighty five pediatricians comprise the attending pediatric staffs of the twenty one hospitals. The number for states varies from three to sixteen, but only four report eight or more. The period of the respective services varies from two to twelve months. Only one hospital reports a service as short as two

months. The majority of the services are for six to twelve months but six report services of three- or four-month periods.

Newborn Service—Fourteen hospitals maintain their newborn service under the supervision of the pediatric department.

Nursing—There is a special nurse in charge of the children's department in each hospital. Fifteen of these nurses have had special pediatric training. Among a few, this training has been for a period of only two three or four months. Nineteen hospitals have student nurses. Their average time of service usually is from two to four months. The average student nurse has from two to ten infants under her care, and, when she is in the children's department she will care for from three to ten children.

Social Service—Seven hospitals have a special social service for children.

Diet Kitchen—Fourteen hospitals have a special diet kitchen for infants, and eleven have one for children.

Schooling and Recreation—Schooling for convalescents is provided in four hospitals and recreation in five.

Dispensaries—Nineteen hospitals maintain a dispensary for children. With only a few exceptions these clinics are open daily with attendance varying on the average from twenty-five to fifty patients. In a few instances the attendance figure is from ten to twelve patients. In fourteen instances the same staff serves in both hospital and dispensary. Residents serve in the dispensary in six of the ten hospitals having residents, and internes serve there in thirteen instances.

Table II presents figures concerning admissions, deaths, autopsies and percentage of deaths and autopsies.

TABLE II

YEAR 1933

STATE	NUMBER ADMITTED		DEATHS		AUTOPSIES		PERCENTAGE		PERCENTAGE	
	NEWBORN	CHILDREN	NEWBORN	CHILDREN	NEWBORN	CHILDREN	NEWBORN DEATHS	NEWBORN AUTOP	CHILDREN DEATHS	CHILDREN AUTOP
Ala.	2,091	2,817	84	163	18	40	4.0	21.4	7.3	24.5
Fla.	1,088	430	25	71	4	13	2.4	16.0	16.6	18.1
Ga.	1,434	883	38	62	5	11	2.6	13.1	5.8	21.1
Ky.	2,998	2,590	130	229	50	68	5.4	30	8.8	29.3
La.	3,102	15,277	171	420	No reply	No reply	5	--	3.2	-
N. C.	615	1,143	32	62	20	41	5.4	81.2	5.4	66.1
Okl.	760	1,379	45	156	10	67	1.1	22.2	11.3	42.8
S. C.	621	901	41	91	5	14	7.8	12.1	10.0	15.3
Tenn.	1,350	1,181	86	125	19	1	6.3	27.0	10.5	43.2
Texas	806	1,142	62	176	10	35	7.1	16.1	1.4	19.8
Va.	246	376	8	16	2	5	3.2	25.0	3.9	33.3
W. Va.	586	1,010	17	45	2	10	2.9	11.7	4.2	22.2
Total	14,512	26,675	745	1,031	111	384	5.1	20.2	6.1	21.7

Includes necropsies on stillborn.

COMMENT

Comment will be restricted to this report without comparison with the figures of the first report. Comparative figures from all regions will be discussed in a final report.

The fact is somewhat surprising that in this large area comprising twelve states, only twenty one hospitals with pediatric services large enough for consideration in this report are found. Furthermore, among these hospitals there is a seemingly low total of 1,763 available beds and bassinets for infants and children. Several factors probably influence these figures, among them, the economic status, population density, and possibly some backwardness in developing better pediatric departments in the hospitals in this region.

Six hospitals have a pediatric department which they consider large enough and of sufficient importance to warrant the employment of a full time resident. Ten report that they have a pediatric resident, but in four instances he does not serve exclusively in the pediatric department.

Four hospitals offer special pediatric internships, and among sixteen institutions offering a pediatric service as part of a general rotating internship, the usual time spent on the service is from one to two months. A rather limited pediatric knowledge would be acquired in one or even two months.

All hospitals have attending pediatricians. There is a total number of eighty five for the entire area, or about four per state. There are considerably more than eighty five pediatricians in Region II. Allowing for a large group who confine their hospital staff associations to children's hospitals, there must remain another considerable group who do not have an opportunity to serve in pediatric departments of sufficient size to afford them valuable experience.

Newborn services should be under the complete or at least partial supervision of the pediatric department but are not in seven of these institutions.

Nursing is apparently supervised in each of the twenty one pediatric services by a graduate nurse. However, according to our information, six of these nurses have not had pediatric training, and among a few their special pediatric training has been for two short periods of time to be of much value.

Pupil nurses are trained in nineteen hospitals, and the extent of their pediatric training is about the same as that in any general nursing course, that is from two to four months.

One third of the hospitals maintain a social service department for children, two thirds, a special diet kitchen for infants, one half, a diet kitchen for children. These figures are gratifying when one considers that many of the children's services are relatively small.

Schooling and recreation for convalescents do not receive much emphasis among these hospitals. Less than one fifth provide schooling, and less than one fourth, recreation.

All hospitals but two maintain a children's department in the dispensary, and in general the attendance is good, often being thirty or forty children per day. In two thirds of the hospitals, the same pediatric staff serves both hospital and dispensary, but internes and residents are in service there in too few instances.

You may draw your own conclusions after perusal of Table II. We merely point out that the total number of children and newborn receiving care in these hospitals during one year is not large. The newborn death rate is commendably low in some and much too high in others. The autopsy percentage figures for both children and newborn show considerable room for improvement in most instances.

Academy News

The Region I meeting of the American Academy of Pediatrics will be held Friday and Saturday Oct. 11 and 12 1935, at the Bellevue-Stratford Hotel, Philadelphia, Pa.

Dr S. Herman Lippitt, Milwaukee, Wis., who had just been elected to Fellowship of the Academy Dec. 1, 1934, died suddenly Dec. 7 1934 of heart disease

Dr Roger H. Dennett, New York, N Y died of heart disease Feb 3 1935 Dr Dennett was born fifty-eight years ago in Boston and took his medical degree at Harvard University He was the author of several books and a contributor to the Journal

Dr E. J. Hoenekens, Minneapolis, has accepted the state chairmanship for Minnesota.

Erratum

In the article, 'A Statistical Analysis of Whooping Cough Cases,' by John A. Toomey, M.D., which appeared in the September 1934 JOURNAL OF PEDIATRICS, the last sentence in paragraph 3 should read, 'In our series, 87.7 per cent (instead of 87.3 per cent as published) of the deaths occurred during the first two years'

News and Notes

The eleventh session of the International Association for the Promotion of Child Welfare will be held at Brussels, July 25 to 29, 1935

There will be four sections social, juridical, pedagogic, and medical Among the questions for discussion at the medical section are The status and needs of pediatrics in the medical organization, infant mortality caused by the diarrheas, immunization against tuberculosis in infancy, and the training of the infant

The meeting will be held in connection with the International Exposition in Brussels in 1935 Detailed information may be obtained from the secretary, Dr J Maquet, Ave de la Toison D'Or 67, Brussels

The pediatricians of Louisville under the auspices of the American Academy of Pediatrics will give a practical postgraduate course in pediatrics on each Wednesday beginning April 24 and running through to July 1 The lecturers will utilize the patients in the Children's Free Hospital where the course will be held The hours will be from 9 to 12 A M and from 12 30 to 1 30 P M which will enable men living from 75 to 100 miles from Louisville to put in intensive work and get back home in time to take care of any necessary calls The charge of the course will be \$5 Correspondence should be directed to Dr Philip F Barbour, state chairman.

The Children's Free Hospital also extends an invitation to any doctor visiting Louisville to spend a day or week in the hospital wards getting acquainted in this way with the newer developments in pediatrics

The following men have been certified by the American Board of Pediatrics since the last report

Edward Dyer Anderson, Minneapolis, Minn
William Willis Anderson, Atlanta, Ga
Harry Calvin Berger, Kansas City, Mo
Urban J Busiek, Springfield, Mo
Gerald M Cline, Bloomington, Ill
William Orin Colburn, Lincoln, Neb
Joseph B Cowherd, Kansas City, Mo
Vincent Del Duca, Camden, N J
Daniel James Dolan, New York, N Y
David Gingold, Brooklyn, N Y
Roy Edward de la Houssaye, New Orleans, La
A Wilmot Jacobsen, Buffalo, N Y
Carl O Kohlbry, Duluth, Minn.
Peritz M Kurzweil, New York, N Y
Sylvan Daniels Lazarus, Brooklyn, N Y
Robert Holmes McBride, Sioux City, Iowa
Ralph W McKelvy, Los Angeles, Calif
Ellsworth Moody, Joplin, Mo
C Ulysses Moore, Portland, Ore

Ralph E. Netzley, Pasadena, Calif.
Henry C. Niblack, Chicago, Ill.
John Mott Rector, San Francisco Calif.
Phillip Elias Rothman, Los Angeles, Calif.
Henry Larned Keith Shaw Albany N Y
Donald C. Shelby, Los Angeles, Calif.
Carl H. Smith, New York, N Y
Oliver Linwood Stringfield Stamford Conn.
Sidney H. Weiner, Boston, Mass.
Edwin Theodore Wyman, Boston, Mass.

Book Reviews

An Atlas of Infant Behavior ARNOLD GESELL, PH.D., M.D., Sc.D. Volume I, Normative Series (in collaboration with Helen Thompson and Catherine S. Amatruada), Volume II, Naturalistic Series (in collaboration with A. V. Kelher, F. L. Igg, and J. J. Carlson) Loose leaf with over 3,000 photographs Yale University Press, New Haven, 1934

Infant Behavior, Its Genesis and Growth ARNOLD GESELL AND HELEN THOMPSON, McGraw Hill Book Company, Inc., New York, 343 pages, 1934

This Atlas is an outstanding contribution in the field of infant behavior. It is not only a unique but a most important contribution. All students of infant development and behavior are familiar with Dr. Gesell's work and methods of study. In these two volumes some 3,000 action photographs have been selected from the thousands of feet of film records made in recent years by Dr. Gesell and his associates in the Clinic of Child Development at Yale University.

Volume I, *Normative Series*, portrays the systematic development by lunar month intervals of postural development, locomotion, and various forms of adaptive behavior, thus the behavior pattern of the infant in the prone, sitting, and standing positions is shown month by month. Such adaptation patterns are shown as the use of the cup, and cubes, as well as more complicated patterns in older infants, as the use of ring, string, and bell. A study of the pictures shows the growth and development of behavior month by month far more clearly and graphically than could ever be possible by description.

Volume II, *Naturalistic Series* portrays in a similar way the behavior of normal infants under the ordinary natural conditions of home life. The behavior patterns of feeding, the bath, play, and certain social relationships are portrayed as they develop month by month.

The mechanical make up of the book is excellent. The photographs, which are enlargements from 16 mm. and 35 mm. cinema records, are clear and excellently reproduced. Each photograph has a brief explanatory note. Only one side of the page is used, and, as the pages are bound in loose leaf, they may be separated and regrouped according to the needs and desires of the individual student. The reviewer is overwhelmed with the obvious painstaking, time consuming detail with which the pictures have been studied, selected, and finally brought together in this Atlas. It can be stated without exaggeration that the Atlas is monumental in character and the possibilities of its use in teaching and research are tremendous. Everyone interested in the field of infancy can take a just pride that such a work has come from an American clinic.

Infant Behavior was published at the same time as the Atlas and has a definite relationship to it. It summarizes the behavior characteristics in some twenty five situations in infants from the fourth to the fifty sixth week. After two chapters devoted to the objects and methods of study, a detailed description of the behavior pattern in the various situations follows which makes up the larger part of the book. Concluding chapters are "The Ontogenetic Patterning of Behavior," "Mental Growth and Maturation," and "The Developmental Diagnosis of Infant Behavior."

No attempt has been made in either the Atlas or accompanying volume to develop a scale of norms. What the authors have been presenting is factual data. A study of the pictures of the Atlas gives a much clearer picture of the development of infant behavior than has ever been given before. The work is of importance to podiatricians as well as to those whose field is limited to the study of infant and child development.

B. S. V

The Crippled and Disabled. HENRY H. KESSLER, Columbia University Press, New York, 1935, p. 337

The author defines the problem of the disabled as that of vocational maladjustment. He divides the disabled into five groups: the cripple child, the industrially disabled, the war disabled, the chronically disabled through disease and the group disabled through blindness and loss of hearing. The problems and remedial measures in general are discussed for each group and the various state and federal measures in force or enacted by the legislatures are given in detail. It is a most timely volume in view of the tremendous interest in social insurance, pensions and similar matters now occupying public attention. The author has collected a mass of information which is ably analyzed and presented in a clear direct manner.

Comments

THE legislation involving "social security" which has been proposed at Washington and concerning which hearings are now being held before congressional committees is of fundamental importance to the medical profession. The *Journal of the American Medical Association* has recently outlined the proposed legislation, and a special meeting of the House of Delegates has been called to discuss the matter. The measures proposed, if passed, will inevitably be the beginning of marked changes in the character of medical practice in the United States.

Certain measures have been proposed relating directly to the field of child welfare. Some of these measures will undoubtedly be opposed by the American Medical Association. The Academy of Pediatrics has taken no official stand in these matters although some pediatricians as individuals are supporting the child welfare measures. In brief, the child welfare measures propose an expanded program for mothers' pensions, federal cooperation in providing protection and care for homeless, dependent, and neglected children, federal aid in expanding maternal and child health programs, and care of the crippled child. The last two items in particular call for matching state funds and provide that state programs shall be approved by the Children's Bureau. This involves the old questions which were raised in opposition to the Sheppard Towner Act.

CONSIDERABLE confusion exists in regard to the Child Labor Amendment, which is being so bitterly fought in many of the state legislatures. Unfortunately many people who do not understand the situation look upon those opposed to the amendment as being in favor of child labor. This is quite contrary to the truth. There are many individuals opposed to the amendment who are bitterly opposed to child labor. The opposition lies in the vagueness and in the unlimited power which the amendment gives to a bureaucracy at Washington. While the extreme powers which the amendment permits as depicted by some of the opponents are absurd, there is a possibility of an abuse of power which is real and not a "straw man." The writer of this is personally opposed to child labor and also to the child labor amendment—a stand that has been difficult to make clear to members of some of the women's clubs who have passed resolutions in favor of the amendment on the commendable grounds of its doing away with child labor. As a matter of fact, since the necessity for the amendment is the thing we cannot see, why establish a situation which may lead to trouble? The value of the amendment is all the more questionable in our mind in view of the recent statement of President Roosevelt that one of the real accomplishments of the New Deal was the doing away with child labor.

What irritates most is the necessity of explaining in detail that we are against child labor when we say we are not in favor of the child labor amendment. It's not the goal but the means to the end that is questioned. The proponents of the amendment unfairly classify opposition to the amendment as favoring child labor.

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STUDIES IN FAT METABOLISM

I FAT ABSORPTION IN NORMAL INFANTS

J. EMMETT HOLT, JR. M.D. HERBERT C. TIDWELL, Ph.D. CLAUDE M. KIRK M.D. DOROTHEA M. CROSS AND SARAH NEALE, BALTIMORE, MD

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Introduction

CONFLICTING opinions have been held by pediatricians as to the value of particular fats in infant nutrition. Some have maintained that, aside from their vitamin content, all fats were alike and were valuable only as sources of energy. Others have attributed a physiologic significance to the chemical differences between natural fats, quite popular has been the belief that the fat of human milk represented an ideal, peculiarly suited to the needs of the infant, and no little effort has been expended in devising imitations of this for use in artificial feeding. The evidence in favor of this latter view has been scanty and for the most part unconvincing. Recently, however, there have appeared a number of isolated observations¹ which lend support to the view that fats are not alike physiologically and suggest that some of their components may perform functions hitherto unsuspected. This has made it seem desirable to reinvestigate the question of the comparative value of different fats from as many points of view as possible, and it was with this in mind that the present work was undertaken.

An adequate comparison of different fats should involve not only a study of their ease of assimilation but should also cover their fate after absorption. It is quite possible that fats behave differently in their effect on respiratory metabolism, in ketogenesis, on water metabolism, in immune reactions and in their hemolytic properties. It is possible that differences exist in the ease with which intolerance can be produced by overfeeding with different fats. Some of these questions we are investigating and will report on subsequently. The present report, however, will deal only with our observations upon absorption from the intestine. Such conclusions as can be drawn from this part of the study in regard to the value of different fats are only tentative and may be considerably modified by further work upon other aspects of fat metabolism.

The literature on comparative fat assimilation is very extensive, observations have been made on children, adults, and experimental animals, and conclusions have been drawn from clinical data, from alimentary hypemic curves, and from balance experiments in which retention has been accurately measured.

Numerous clinical observations have shown that infants will thrive upon a great many different fats, provided that their vitamin requirements are not neglected. Aside from the animal milk fats, animal body fats have been used—suet, lard, tallow, chicken fat, goose fat, egg yolk, and fish oils, notably cod liver oil. Among the vegetable oils, olive oil has been the most extensively used, but there are also reports in which corn oil, cotton seed oil, peanut oil, soy bean oil, sesame oil, cocoanut oil, cocoa butter, and palm oil have been fed, as well as

various mixtures of animal and vegetable fats. No convincing evidence has as yet been adduced that one fat is better handled than another. Only in rare instances was the same infant studied on diets in which the only variable was the fat. Most of the observations were uncontrolled and were continued for relatively short periods. Moreover, in interpreting such clinical reports, it is difficult to eliminate the bias of the observer and the particular care which the subject of an enthusiastically conducted feeding experiment is likely to receive. Such conclusions as have been drawn must be classed as impressions; but, among the conflicting impressions recorded, it is worthy of comment that more than one observer² has reached the conviction that olive oil is superior to butter fat at least as far as gain in weight* is concerned.

The data from alimentary lipemic curves are scarcely more conclusive. Lipemia has been followed by chemical methods and by the somewhat less accurate procedure of counting the number of fat particles in an ultramicroscopic field. Only a few observations are recorded in which different fats were studied with an identical technique. Rony and Mortimer²⁴ reported that oral administration of egg yolk to dogs caused a more prompt rise in the blood lipids than did olive oil. The comparisons were apparently not made in the same individual subjects. McArthur,²⁵ in a small series of adults, using the ultramicroscopic technique noted that lipemia developed most rapidly after ingestion of cod liver oil, somewhat less rapidly after butter, and least rapidly after goat's milk fat. Schroeder and Evelyn Holt⁴ using the ultramicroscopic method made numerous observations on infants. Unfortunately, in many of their experiments the quantity as well as the nature of the fat was varied, a fact which lessens the significance of some of their results. They did find very definitely that a commercial preparation of oleomargarine gave a negligible postabsorptive lipemia as compared with butter or breast milk fat, a fact which they attributed to poor absorption of the oleomargarine. Little reliance can be placed upon the alimentary lipemic curve as an index of fat absorption. The level of the blood fat is determined by the rate of removal of fat from the blood as well as the rate at which it is introduced. The alimentary lipemic curve is notoriously capricious, and it is by no means uncommon to find, both in young children⁵ and in adults^{4, 7} individuals who show no postprandial rise, even under circumstances which make

How erroneous a conclusion can be drawn when gain in weight is used as the sole criterion of absorption is well illustrated by some comparisons we made upon three infants fed first on butter fat and then on the ethyl esters of butter fat. When the ethyl esters were substituted for the triglycerides for a period of twelve days, all three children gained weight more rapidly and continued to exhibit every sign of health. Nevertheless the retention of fat (figured as percentage of intake) was only 39.3 per cent, 48.3 per cent, and 44.7 per cent, respectively, on the ethyl ester periods as compared with 51.3 per cent, 51.7 per cent, and 84.8 per cent on the butter fat periods. The greater gain in weight may have been a temporary effect due to water retention, which is known to occur when the proportion of carbohydrate to fat absorbed increases. Without the metabolism data one might well have concluded that the ethyl esters were superior to the triglycerides.

it reasonably clear that fat is being absorbed. This phenomenon is more likely to be met with when the quantity of fat given as the test meal is comparable to that of the usual diet and would seem to be due to removal of fat from the blood as rapidly as it is introduced. It is, therefore, possible that a pronounced alimentary lipemia, such as was noted by McArthur after the administration of cod liver oil, may find its explanation in a difficulty of removal of fat from the blood rather than in a more prompt entrance. And, conversely, the failure of alimentary lipemia, noted by Schroeder and Holt⁴ after the administration of oleomargarine, may have been due to the ease with which absorbed fat was removed from the blood rather than to diminished absorption.*

To date the only reliable information in regard to the absorption of different fats has been obtained from balance experiments. Experiments on adults and on experimental animals have yielded certain

TABLE I
FAT RETENTION ON COW'S MILK AND BREAST MILK
(FROM DATA OF HOLT, COURTNEY AND FALES)

	PERCENTAGE OF FAT INTAKE RETAINED	PER CENT DISTRIBUTION OF FECAL FAT		
		NEUTRAL FAT	PATTY ACID	SOAP
Average of 8 infants on breast milk	95.8	19.7	27.7	52.6
Average of 28 infants on cow's milk*	90.7	9.6	14.4	76.0

*The figures given here for infants fed on cow's milk differ slightly from those given by the authors in their summary. Reference 12 Tables IX and XVIII. The reason for this is that we have excluded from the series certain infants who received supplements of olive oil.

more or less definite facts, such as a relation between melting point, the degree of unsaturation, the length of the carbon chain, and fat absorption. These will be more fully discussed later in this paper.

The pediatric literature of the last fifty years contains numerous studies on fat metabolism but almost none in which different fats were compared under identical conditions. Holt, Courtney, and Fales⁸ compared nut butter and corn oil with butter fat in older children, finding no striking differences. With the exception of Frontal,⁹ who substituted olive oil for butter in the Czerny-Kleinschmidt butter-flour mixture and found fat retention somewhat improved, we have been able to find no comparisons of this kind in infants. Many studies have been made on fat retention on cow's milk as compared with breast milk, which studies have in the main confirmed the original findings of Uffelmann.¹⁰ The difference is clearly illustrated by the data of

*Our own metabolism experiments lead us to believe that the latter interpretation is probably the correct one. Although we have not been able to ascertain just what brand of oleomargarine was used by Schroeder and Holt, it has been our experience with preparations on the American market that these are absorbed practically as well as butter fat. This was also the experience of Holt, Courtney, and Fales.⁸

Holt, Courtney, and Fales^{11 12} summarized in Table I. Fat retention is noticeably higher on breast milk, and there are differences in the partition of the fecal fat—the stools on cow's milk containing a higher proportion of soap and less neutral fat and free fatty acid.

The difference in fat retention on cow's milk and on breast milk is not great, but considerable significance has been attached to them. Scarcely an authoritative work in pediatrics is to be found which does not comment upon the relatively difficult digestibility of cow's milk fat, and this doctrine has been responsible for the general abandonment of the cream and top-milk mixtures that were so popular a generation ago. Today the usual practice in artificial feeding is to give not more than 35 per cent of the calories in the form of fat, in contrast to breast feeding in which the infant receives approximately 50 per cent of his calories as fat. A surprising amount of work has been done in devising feedings to obviate one or another of the differences between cow's milk fat and breast milk fat or the factors supposed to affect fat absorption—all without any clear and definite knowledge as to which of these factors was responsible for the difference in retention. Among the procedures used to imitate breast milk may be mentioned (1) the substitution of various animal and vegetable fat mixtures for butter, in order to emulate the physical and chemical constants of breast milk fat (2) heating butter to drive off the volatile fatty acids, (3) homogenization of milk to decrease the size of the emulsified fat particles and (4) demineralization of the milk to diminish the loss of fat as soap in the stools. Most of these procedures are rational and have some experimental basis of fact, but the data in regard to their significance are so conflicting, and so little attempt has been made to study the factors individually, that we undertook to conduct a series of experiments in children in which only one factor at a time was varied.

Experimental Methods

Preparation of Feedings—In all of our studies designed to compare different fats, a standard basal feeding made from fat free milk powder, water, and cane sugar* was used. The fat constituting about 4 per cent of the final diet by weight was incorporated in the reconstituted skim milk by homogenization,† a standard homogenizer of the Gaulin type being used at 4,000 pounds pressure. The feeding was then autoclaved at about 15 to 20 pounds pressure for half an hour.

Technic of Metabolism Experiments—These were carried out upon normal male infants between six weeks and eight months of age, who

*The added cane sugar constituted about 8 per cent of the final feeding with the exception of subjects K—n, G—n and H—t, whose feedings were prepared with the addition of only 5 per cent of cane sugar.

†We wish to take this opportunity of thanking Dr. J. H. Shrader of the National Dairy Products Research Laboratories, for permission to use their homogenizing apparatus, and also Dr. R. Whitaker of the same laboratory for assistance in homogenizing the mixtures.

were placed upon frames designed to permit the separate collection of urine and feces. The metabolism periods were in most instances six days in length and were preceded by a foreperiod of one to four days on the identical diet. In our earlier experiments the stools were marked at the beginning and end of the period by means of charcoal or a dye, such as carmine or vital red, but we subsequently abandoned this procedure when the experimental period was six days or longer, as it seemed to add little to the accuracy of the experiment and the presence of the dye was found to be an inconvenience in the titration of fatty acids.

Analytical Methods—The determination of total lipids in the food and feces, and of fat partition in the latter, was carried out by a modification of the procedure of Holt, Courtney, and Fales¹³ which some of us have described elsewhere¹⁴.

Iodine Value—The method of Wijs¹⁵ was used for determinations on fats and fatty acids. Determinations made on unsaponifiable material were done by the pyridine bromide method¹⁶.

Thiocyanogen Value—The method of Kaufmann¹⁵ was used. It was found that the determinations of iodine value and thiocyanogen value were unreliable when more than a trace of unsaponifiable matter was present. On this account the determinations of constants on the fecal fat were made upon the fatty acids rather than the total lipids of the feces. In the calculations of the per cent of linoleic, oleic, and saturated fatty acids, the following formulas given by Jamieson¹⁵ were used:

$$\begin{aligned}\text{Per cent linoleic acid} &= \frac{1104}{1112} (I, \text{No} - \text{SCN No}) \\ \text{Per cent oleic acid} &= \frac{1112}{1112} (2 \text{ SCN No} - I, \text{No}) \\ \text{Per cent saturated acids} &= 100 - (\% \text{ linoleic} + \% \text{ oleic acids})\end{aligned}$$

Experimental Observations

I THE INFLUENCE OF THE SIZE OF FAT PARTICLES ON FAT RETENTION

We have already mentioned the prevailing view among pediatricists that fine subdivision of the fat particles favors fat assimilation, but it may be of interest to examine the sources of this idea. In the first place, emulsification is known to occur normally during digestion of fat, and it is logical to suppose that any assistance in this direction will lighten the work of the body and thus be beneficial. In the second place, the superiority of breast milk to cow's milk in infant feeding has often been attributed to a finer fat emulsion. Most English and American textbooks¹⁷ on pediatrics and infant nutrition carry statements to this effect, of which the following two, taken from recent publications, may be quoted. According to Garrod, Batten, Thuisfield, and Paterson,¹⁷ "much of the indigestibility of cow's milk is due to the fat, the globules being 10 to 15 times as large as those of breast milk." McLean and Fales^{17a} in discussing breast feeding and

artificial feeding state that "the fat globules of breast milk are small, therefore easily attacked by the digestive juices" Similar statements are to be found in the continental literature although the testimony on this point is not entirely unanimous.¹⁸ Lastly there are clinical reports¹⁹ in which improvement has followed the use of homogenized milk, the fat particles of which are far smaller than those of any natural milk.

None of this evidence will bear critical analysis. Though it is granted that emulsification occurs normally in the process of fat digestion there is nothing to indicate that the infant finds difficulty in performing this function himself. Unemulsified fat rarely appears in the feces and when it does so, this can usually be attributed to some gross defect such as absence of the external secretion of the pancreas. A fine emulsion is not a prerequisite for fat splitting, for as Rona and Kleinmann²⁰ have shown the rate of lipolysis is independent of the size of the fat particles.

As regards the relative size of the fat globules in breast milk and cow's milk, we recently examined several specimens of each under the microscope and were astonished to find that we could not distinguish between them. We then turned to the literature to find the original data upon which the commonly accepted statement is based. It appears that only a few accurate comparisons of the two milks have been made from this point of view. Rough estimates of particle size date back to the pioneer observations of Donné²¹ in 1837, but accurate measurements with counts of the numbers of particles of various sizes have been made only since 1895 when Gntzer²² introduced an accurate counting apparatus. Although many of the earlier workers had reported gross differences in particle size some finding those of human milk to be far smaller and others far greater than those of cow's milk since the introduction of the refined measurements such differences as have been found have been very small indeed;²³ the variations between different breeds of cows and between individuals are greater than the species variations. Both milks contain particles from 0.3μ up to 10μ , with occasional particles as large as 20μ in diameter. The bulk of the fat consists of particles between 2μ and 5μ in size. The more recent reports such as that of Washburn and Jones,²⁴ indicate that the average and the extreme size of human milk particles is about the same as in Holstein milk and slightly less than in Jersey milk.* It is thus

The figures obtained by Washburn and Jones were as follows:

	MINIMUM SIZE (μ)	MAXIMUM SIZE (μ)	AVERAGE SIZE (μ)
Average of 4 human milks	0.3	8.8	2.20
Herd milk (Holstein)	0.34	9.13	2.14
Herd milk (Jersey)	0.53	10.00	3.81

The slightly larger size of the particles in Jersey milk can be attributed to its higher fat content. Samples of milk containing more fat exhibit particles of slightly larger average size. In making comparisons between different species, it is important that the samples studied should contain approximately equal quantities of fat.

apparent that any superiority human milk may possess for infant feeding is not due to the size of the fat emulsion

Turning now to the evidence obtained from feeding homogenized milk, we find conflicting testimony. Some pediatricians like Variot^{19b} and Ladd^{19c} are enthusiastic, whereas others²⁵ are not impressed. Laboratory observations have failed to settle the question. Washburn and Jones²⁴ conducted a series of feeding experiments on homogenized milk with young pigs, but the results were so confusing that they were finally forced back to the conclusion that homogenized milk was probably superior because of the gross appearance of the curd, which looked as if it would be easier of digestion. A few observations on fat retention in infants fed on homogenized milk have been made. Chevalier²⁶ reported improved retention in six infants on this feeding. Usuki,²⁷ on the other hand, in a single experiment found that absorption was somewhat poorer with homogenized milk. Ladd^{19c} refers to some experiments carried out by Laws in Bloor's laboratory which confirmed him (Ladd) in his high opinion of homogenized milk. Details of these experiments have apparently not been published, and we have not succeeded in obtaining further information about them.

Since the question of the effect of particle size on fat absorption is apparently not settled, we undertook to study this. In our experiments we attempted to vary the size of the particles as widely as possible, three different feedings were employed: (1) homogenized cow's milk, (2) unhomogenized cow's milk, and, (3) fat-free cow's milk to which the appropriate amount of fat was added in unemulsified form as melted butter, being either fed by spoon or introduced into the baby's mouth with a syringe. The proportion of fat given was approximately the same in all three feedings. Table II shows the results obtained.

It is apparent that minute subdivision exercised no favorable influence on fat absorption. Differences between the homogenized and unhomogenized milk feedings are altogether negligible. Curiously enough the infants receiving unemulsified fat showed a slightly higher retention than did the other two groups. In part this was probably, due to the fact that this particular group included no very young infants, whose retention is appreciably poorer. It is also possible that the difference is due in part to experimental error, for the measurement of the fat intake was not quite as accurate in the experiments with unemulsified fat. Certainly emulsification of the fat fed is unnecessary and adds nothing to the digestibility of the fat.*

*In the experiments described above it should be noted that autoclaved milk was used throughout. Homogenization can however be carried out without heating milk to temperatures that wholly or partially denature the proteins. Under these conditions the fine subdivision of the fat alters the character of the protein curd and may increase its digestibility as compared with raw milk receiving no such thermal treatment. Our experiments do not bear upon this point; they were designed to show only the effect of size of fat particles on fat digestion, with the factor of indigestibility of the protein curd ruled out.

II THE EFFECT OF OTHER FOOD CONSTITUENTS UPON FAT RETENTION

A. *Minerals*—Although some evidence²² of an inverse relationship between soapy stools and fat retention had already been obtained, attention was more strongly focused upon the effect of mineral intake by

TABLE II
INFLUENCE OF SIZE OF FAT PARTICLES ON FAT RETENTION

PERIOD	AGE (MO.)	WT. (KG.)	LENGTH OF PERIOD (DAYS)	FAT INTAKE (GM./DAY)	FECAL FAT				FAT RETENTION		
					GM./DAY	PARTITION			GM./DAY	% OF INTAKE RETAINED	
						% X F	% F F A	% SOAP			
Homogenised Cow's Milk											
G-n	2	2	8.60	5	20.64	3.58	3.4	20.8	75.8	17.06	82.7
G-n	7	8½	4.25	5	20.60	2.88	8.7	32.8	63.6	17.64	87.0
K-n	2	1	4.65	8	25.56	8.74	7.2	13.9	78.8	21.82	85.4
K-n	8	3	6.65	4	23.89	8.88	15.1	17.6	69.8	20.05	84.0
H-t	2	2½	4.80	8	27.85	4.79	8.9	15.1	78.0	28.07	82.8
McK-a	1	7½	5.85	8	26.25	3.17	15.2	9.8	77.0	24.08	91.7
McK-a	4	9½	3.85	6	52.90	4.18	18.4	10.0	65.5	28.72	87.8
M-r	1	3½	4.35	8	21.00	1.82	10.6	12.6	76.8	19.18	91.8
M-r	9	6½	7.05	5	81.60	3.05	8.4	9.9	81.7	28.55	90.3
W-d	1	4½	5.15	5	50.70	4.63	5.3	26.1	68.5	26.02	84.8
W-d	8	5½	6.00	8	31.50	3.66	7.4	28.5	66.1	27.84	88.4
F-r	3	2½	3.55	0	15.75	1.48	18.9	14.8	55.5	14.22	90.9
F-r	7	4	4.35	6	20.50	3.14	9.1	11.6	79.3	18.38	89.6
K. J-n	5	4	5.40	6	26.80	1.77	10.6	15.8	73.8	24.56	93.8
J S-h	18	9	8.16	6	87.01	5.85	9.9	14.7	75.4	38.18	89.8
W S-h	14	9	7.98	6	32.96	2.92	8.4	14.5	77.1	30.05	91.1
H-k	3	5½	4.70	6	24.91	3.34	7.3	18.4	74.3	31.57	86.8
F-r	1	3	4.96	8	25.14	2.87	18.4	18.7	69.9	22.27	88.5
W-r†	1	5½	4.80	6	23.18	2.65	7.9	22.8	69.3	22.53	89.8
B-s	1	3½	5.23	5	23.25	2.46	11.8	26.4	62.0	20.79	89.4
O-t	2	4	5.38	8	35.10	4.61	6.8	43.0	50.2	30.49	86.9
Average		4½	5.59	6	36.58	3.15	9.7	18.6	71.4	25.44	88.2

Unhomogenized Cow's Milk

G-n	1	2	3.43	5	20.62	3.00	5.5	29.4	65.1	17.82	85.5
G-n	18	8	4.40	4	26.85	3.26	4.5	12.7	82.8	20.59	88.4
K-n	1	½	4.33	5	25.18	4.46	4.7	18.5	76.8	20.75	82.4
K-n	14	6½	7.15	4	28.18	4.41	5.4	10.2	84.4	21.72	83.1
H-t	1	2	4.40	10	28.00	2.85	8.2	16.5	75.3	25.15	89.8
H-t	11	8½	8.90	5	28.29	2.88	8.9	10.8	80.8	25.92	91.8
<i>Average</i>		4	5.10	5½	25.35	3.59	6.2	16.4	77.4	21.96	86.5

Unemulsified Butter Given by Spoon or Syringe

G-n	12A	5½	4.88	4	24.90	1.93	4.9	21.3	73.7	20.07	90.3
G-n	12B	5½	4.40	4	24.90	1.92	7.6	14.3	78.1	22.08	92.3
K-n	12A	6	7.05	4	25.00	2.49	8.2	16.0	77.7	22.71	90.0
K-n	13B	6	7.14	4	25.00	2.10	9.9	11.8	77.9	22.90	91.6
H-t	10A	8½	8.80	4	25.16	1.98	7.7	17.1	75.2	24.08	95.7
H-t	10B	6½	8.84	4	25.18	2.23	10.4	11.5	78.1	22.03	91.2
F-r	12	5½	5.07	6	21.60	1.06	24.9	35.8	38.3	20.54	95.1
K. J-n	10	5½	6.67	6	27.60	1.85	20.0	8.0	72.0	25.75	93.3
<i>Average</i>		6	6.04	4½	24.95	1.83	11.5	17.1	71.4	23.08	92.7

Discharge from ear. Infant gained well
slight nasal discharge for two days

the observations of Bowditch, Bosworth, and Giblin²⁹ in 1918. These authors concluded that even cow's milk provided an undesirably high mineral intake, its high calcium content causing considerable loss of fat in the feces as insoluble calcium soaps. Bosworth²⁹ suggested a decalcified milk to avoid this difficulty. Holt, Courtney, and Fales³⁰ in a preliminary report failed to confirm the striking observations of Bowditch and his collaborators. Their own data showed no great loss of soap on high calcium diets, and they concluded that "serious" loss of fat in the stools on cow's milk does not seem to occur. In a later publication³¹ they presented extensive data on calcium and fat retention but did not analyze them from this point of view, being then concerned with the effect of fat upon calcium utilization and excretion rather than with the effect of calcium upon fat metabolism. They did report³² observations on two children to whom a chalk mixture (calcium carbonate) was given as a supplement, in one subject the fat retention was improved, in the other the reverse was the case. Frontali³³ carried out a few experiments with mineral supplements. To one child he gave as much as 5 gm. of calcium lactate a day without noticeable impairment of fat retention. It thus appears that the evidence in regard to the effect of minerals on fat retention is conflicting.

Our own experiments were planned to answer the question: How much of the difference in fat retention on breast milk and cow's milk is due to the mineral intake? Studies were made in which this was the only variable. In the first series of experiments butter fat was used and three levels of mineral intake were compared: (1) a low ash diet, made by incorporating butter in skimmed breast milk, (2) a medium ash diet, made by incorporating butter in skimmed cow's milk, and (3) a high ash diet in which the butter was incorporated in a skimmed cow's milk base, to which a salt mixture* had been added, approximately doubling the content of each mineral constituent.

A second set of experiments was carried out with breast milk fat which was incorporated: (1) in skimmed breast milk, giving a low mineral intake, and (2) in skimmed cow's milk, giving a medium mineral intake. The results of both series are shown in Table III.

The data show very clearly the inverse relationship between mineral intake and fat retention. A part of the known difference between fat retention on whole cow's milk and whole breast milk can be attributed to the difference in mineral content, but this will not

*The high mineral intake was accomplished by the addition of (a) a solution of potassium and sodium phosphates and (b) a solution of calcium chloride and primary calcium phosphate. The final mineral composition of the feeding as contrasted with the normal control milk formula was as follows:

	Na mg / L	K mg / L	Ca mg / L	Cl mg / L	P mg / L
Standard milk formula	13.6	34.2	27.8	25.8	20.0
High mineral formula	26.3	68.4	52.9	56.9	40.0

account for the entire difference, part of which is due to the fat itself. When the two fats are compared with an identical mineral intake, breast milk fat gives the better retention.

We have not investigated the influence of the individual mineral constituents. Evidence in the literature points to the alkaline earth minerals which form insoluble soaps.

Inasmuch as no correlation between calcium intake and fat retention had been attempted by Holt, Courtney and Fales, it seemed worthwhile to analyze their data³¹ from this point of view. In Table IV will be found their data on fat retention as related to the CaO/Fat ratio of the intake in 109 observations on butter fat in normal subjects,

TABLE IV
RELATION BETWEEN CALCIUM INTAKE AND FAT RETENTION
(FROM DATA OF HOLT, COURTNEY & FALES)

RATIO CAO FAT	INGESTED	NUMBER OF OBSERVATIONS	PERCENTAGE OF FAT INTAKE RETAINED	
			AVERAGE	EXTREMES
Normal Infants				
0.021 - 0.040		3	92.1	90.6 - 93.8
0.041 - 0.060		22	89.7	78.9 - 96.4
0.061 - 0.080		5	83.4	70.7 - 94.2
All Normal Subjects				
Below 0.020		6	95.6	94.0 - 97.2
0.021 - 0.040		56	94.3	86.3 - 97.8
0.041 - 0.060		41	91.4	78.9 - 97.5
0.061 - 0.080		5	83.4	70.7 - 94.2
Above 0.080		1	54.4	

thirty of the subjects were infants, the remainder being young children on a mixed diet. Both for the infants and for the series as a whole, the reciprocal relation is apparent. Loss of fat on the diets relatively high in calcium is, as they state, "not serious," but it is nevertheless definite. The data as shown in Chart 1 reveal a certain scattering of the points which is not surprising when one considers that different subjects were used and that the diets were in no sense uniform. On the same graph we have plotted our own average data, which show excellent agreement with those of Holt, Courtney, and Fales. Their results on butter fat average a little higher than ours, a result which may be attributed to the fact that twenty-three of their subjects received small supplements of fat in the form of corn oil, nut butter, olive oil, or cod liver oil.

B Protein—The influence of protein upon fat absorption has been little studied. A few observations have been made on infants whose protein intake was increased by the addition of milk curd to the food. Frontal studied two infants whose diet was supplemented with 25 per cent of plasmon (a proprietary curd preparation), this resulted

in a slight impairment of fat retention Holt, Courtney, and Fales²² stated that some of their lowest retention figures in normal infants were those on patients receiving protein milk, but they did not publish data bearing on this point. Through the courtesy of Miss Fales their unpublished records were made available to us, among which we have been able to find nine experimental periods on five infants who were fed protein milk. These are presented in Table V.

It is apparent that the average fat retention on protein milk (85.7 per cent) is somewhat below that found by the same authors for in

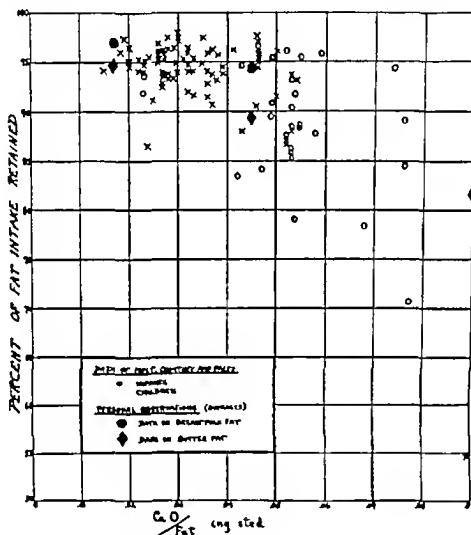


Chart 1.—Relation between CaO/Fat ratio in diet and fat retention.

ants fed on sweet milk mixtures (90.7 per cent). In only one instance was a comparison of protein milk and sweet milk made on the same infant. This patient (A R) showed an increase in fat retention when he was returned from protein milk to sweet milk.

Two possible explanations for the lower fat retention on protein milk suggest themselves. It may be that the protein itself stimulates alkaline intestinal secretions²³ this alkali causing a diversion of fat to the stool in the form of soap. It is also possible that the diminished fat retention is not due to the protein at all, but to the high calcium

TABLE V
FAT RETENTION IN PROTEIN MILK
(FROM UNPUBLISHED DATA OF HOLT, COURTNEY, AND FALES)

CASE	DIAGNOSIS	AGE (MO.)	WEIGHT (GM.)	FEEDING	INTAKE (GM. PER DAY)				% FAT INTAKE RETAINED	
					PROTEIN	FAT	SUGAR	FLOUR		CALCIUM
W G-15	Rickets, marasmus	10	3940	Protein milk, cereal	31.7	15.1	15.7	11.4	1.04	87.8
J J-22g	Convalescent from vomiting and diarrhea	8	4990	Protein milk, sugar, barley flour (raw)	38.4	20.4	24.5	31.5	1.31	89.6
J J-22f	Convalescent from vomiting and diarrhea	8½	4010	Protein milk, sugar, barley flour (raw)	41.5	31.7	26.7	36.0	1.42	85.9
A A-22a	Marasmus	6½	3920	Protein milk, barley flour (raw)	43.7	31.8	19.1	18.0	1.54	80.8
A A-22b	Marasmus	6½	4000	Protein milk, barley flour (raw)	43.7	31.3	18.9	25.4	1.52	85.7
A A-22c	Marasmus	7	4160	Protein milk, barley flour (raw)	42.2	29.8	17.9	30.0	1.45	85.6
A R-10b	Convalescent from marasmus	7½	5300	Protein milk, barley flour (raw)	47.3	31.9	19.2	25.1	1.55	87.9
A R-10c	Convalescent from marasmus	7½	5410	Protein milk, barley flour (raw)	48.0	31.9	19.2	32.2	1.55	85.2
A R-19d	Convalescent from marasmus	7½	5000	Protein milk, barley flour (raw)	44.6	28.9	17.4	38.9	1.40	82.9
Average									85.7%	

Observation on Patient A R After Return to Sweet Milk Formula										
A R-19e	Convalescent from marasmus	8	5680	Sweet milk, barley flour (raw)	24.9	21.6	14.4	45.0	0.74	90.2%

intake. Approximately twice as much calcium is ingested on a diet of protein milk as upon a formula of diluted cow's milk. The magnitude of the diminution of fat retention in the experiments of Holt, Courtney, and Fales was in keeping with the view that this was due entirely to the higher calcium intake. In order to test this point further we studied several infants on diets in which the mineral factor could be excluded, diets in which isoelectric protein—casein or gelatin—was added. The results are given in Table VI.

Inspection of the data reveals no consistent change brought about by the addition of isoelectric protein. The retention of fat is sometimes a little better, sometimes a little worse and at other times identical with that on the control period. One appears justified in attributing the effect of protein milk entirely to its calcium content rather than to any influence of the protein itself. This conclusion is supported by the studies Courtney and Moore²² made upon three infants who were given a synthetic food in which a high protein intake was accomplished by the addition of sodium caseinate. Although the protein content of this food was well in excess of that of protein milk, the diet failed to cause any appreciable falling off of fat retention until the patients developed fever.

C *Carbohydrate*—The claim has been made that starch when given in large quantities exerts an unfavorable influence on fat absorption. Stolte²⁷ studied three infants fed on the Czerny Kleinschmidt butter flour mixture and found low retentions of fat (70 per cent to 83 per cent of the intake). Noack²⁸ obtained similar low figures with this food, but there is reason to believe that his subjects were abnormal, for he obtained even lower retentions on standard cow's milk formulas. Frontal²⁹ made observations on four infants fed on the butter flour mixture who retained 92.6 per cent, 88.3 per cent, 78.8 per cent, and 82.2 per cent of their fat intake respectively (average 85.5 per cent). It seems possible that when starch is used as an emulsifying agent for the fat, as is the case with butter flour feedings, a certain amount of fat may be carried out with undigested starch. On the other hand when starch is added to milk and not used to emulsify the fat (Freund⁴⁰), such loss of fat seems to be negligible. Among unpublished data of Holt, Courtney and Fales, we have found records of observations on four infants who were fed sweet cow's milk with additions of barley flour (from 27 to 45 gm. a day). In these experiments the fat retention was 85.2, 90.2, 90.3, and 87.7 per cent (average 88.4 per cent), figures comparable to those obtained with sweet cow's milk and added sugar.

A few observations have been made on the influence of other polysaccharides and sugars upon fat retention. Uauk⁴¹ studied a number of carbohydrate mixtures but the differences he obtained were not

TABLE VI
INFLUENCE OF PROTEIN ON FAT RETENTION

DIET	PERIOD	AGE (MO.)	WT (KG.)	LENGTH OF PERIOD (DAYS)	INTAKE (GM. PER DAY)		FECAL FAT				FAT RETENTION	
					PROTEIN	FAT	GM./DAY	% N F	% P F A	% SOAP	GM./DAY	% OF INTAKE RETAINED
A Control Periods												
Milk and cane sugar formula	J S-h	13	8.16	6	30.3	37.01	3.85	9.4	14.7	75.4	33.16	89.6
	F-r	1	4.93	6	22.0	25.14	2.87	13.4	16.7	69.9	22.27	88.5
	W-r	1	5.4	6	22.0	25.13	2.56	7.9	22.8	69.3	22.58	89.8
	R. S-h	1*	4.05	5	17.4	19.37	3.29	7.2	20.5	72.3	16.08	83.0
	C-t	2	5.38	6	28.7	35.10	4.51	6.8	43.0	50.2	30.49	86.9
	W S-h	14	7.93	6	27.0	32.96	2.92	8.4	14.5	77.1	30.05	91.1
Average					24.6	29.12	3.55	8.9	22.0	69.0	25.77	88.2
B Periods With Added Protein												
Milk and sugar formula plus isoelectrine casein	J S-h	14	8.40	6	58.6	34.44	3.59	7.8	21.8	70.4	30.85	89.5
	F-r	4	5.93	6	50.3	28.80	2.04	6.9	20.6	72.5	26.76	92.9
	W-r	4	5.80	6	50.2	28.73	2.48	4.0	35.0	61.0	26.25	91.4
	R. S-h	4	4.89	6	41.9	24.00	2.58	9.8	24.8	65.4	21.42	89.2
	C-t	3	5.68	6	54.5	31.98	6.90	9.2	29.5	61.3	25.02	78.3
Plus isoelectrine gelatin	W S-h	15	8.11	6	54.5	34.32	4.20	7.7	27.0	65.3	30.12	87.7
Average					51.7	30.33	3.64	7.6	26.4	66.0	26.74	88.2

*Period terminated one day early because a parenteral infection developed

very striking, his most convincing finding being a somewhat impaired fat retention on a feeding which contained malt soup extract. From *tali*²¹ in one subject found that glucose exercised an unfavorable influence as compared with lactose and maltose. We ourselves have carried out a few experiments designed to compare the effect of cane sugar, lactose and a malt-dextrin preparation (dextrin maltose) on fat retention. The results are given in Table VII.

TABLE VII
INFLUENCE OF VARIOUS SUGARS ON FAT RETENTION

PERIOD		AGE (MO.)	WT (KG)	LENGTH OF PERIOD (DAYS)	FAT INTAKE (GM./DAY)	FECAL FAT			FAT		
						(GM./DAY)	PARTITION			RETENTION	
							% N F	% F F A.	% SOAP		
									GM./DAY	% OF INTAKE RETAINED	
A Cane Sugar											
W—r	1	5½	4.80	6	23.13	2.56	7.9	22.8	69.3	22.58	89.8
F—r	1	3	4.98	6	25.14	2.87	18.4	16.7	69.9	22.37	88.5
R S—h	1	1½	4.05	6	19.87	3.29	7.2	20.5	72.3	16.08	81.0
Average		3½	4.59	6½	23.21	2.91	9.5	20.0	70.5	20.31	87.1
B Dextrinmaltose											
W—r	2	6	5.09	6	24.00	2.40	11.1	20.3	68.6	21.60	90.0
F—r	2	8½	5.25	6	24.00	2.33	12.5	20.4	67.1	21.67	90.4
R S—h†	2	2	4.38	6	19.20	2.43	7.7	17.1	75.2	16.77	87.3
Average		3½	4.91	6	22.40	2.39	10.4	19.3	70.3	20.01	89.3
C Lactose											
W—r	3	6½	5.16	6	25.20	2.45	10.7	30.5	58.8	22.76	90.8
F—r	3	8½	5.55	6	25.20	2.87	11.2	35.5	58.3	22.33	88.6
R S—h	3	2½	4.60	6	21.60	3.16	8.1	30.2	61.7	18.44	85.4
Average		4	5.10	6	24.00	2.83	10.0	32.1	57.9	21.17	88.1

Period terminated one day early because of development of parenteral infection.

†No evidence of respiratory infection *per se*.

No significant difference in fat retention on these different diets is noticeable with the exception of patient R. S—h, who did not retain fat as well on cane sugar as on the other two sugars. This may have been due to the fact that he was affected to a slight extent by the mild parenteral infection which made its appearance at the end of the period. In all three babies the stools contained slightly more free fatty acid in the lactose periods. This is probably due to an increase in volatile fatty acid derived from carbohydrate fermentation, a subject which has recently been studied by Gerstley.⁴²

III THE EFFECT OF VARIATIONS IN THE CHARACTER OF THE FAT ITSELF

A The Presence of Short Chain (Volatile) Fatty Acids—Free fatty acids of 10 carbon atoms or less are volatile with steam. The measure of their presence in a mixed fat is the Reichert Meissl number. In

natural fats this differs widely, for instance, butter contains far more of the short chain acids (R.M. about 30) than does breast milk fat (R.M. less than 2)

Free volatile fatty acids are found in infant's stools, they are slightly more abundant in those of infants fed on cow's milk, in diarrheal states, however, their quantity is greatly increased. Certainly the greater part of the volatile acids of the stool arises from fermentation of carbohydrate, according to one view,⁴³ which has yet to be disproved, they are the irritants which cause peristalsis. But the possibility that some at least of the volatile acids of the stool might arise from their ingestion as such has led to more than one attempt to eliminate fats containing them from the infant's diet. Gerstenberger and Ruh⁴⁴ devised a fat mixture for artificial feeding, in which among other things the Reichert-Meissl number did not exceed that of breast milk. In the preparation of the Czerny-Kleinschmidt butter-flour mixture⁴⁵ the butter is heated until bubbling ceases, the bubbling being presumably caused by the expulsion of volatile fatty acids.*

Our interest lay in determining to what extent, if any, a fat showing a high Reichert-Meissl number is harmful when fed. We attempted to accentuate such effects as these substances might produce by increasing their quantity to approximately twice that of ordinary butter. This was done in two ways: (1) by adding tributyrin to butter and (2) by adding a distillate of free volatile acids obtained from another lot of butter. On neither feeding were clinical disturbances noted, the children remaining quite normal. The tributyrin imparted a bitter taste to the milk so that it was necessary to accustom the babies to it gradually, but once this was done it was well taken. The test given was probably a more exacting one than would have been the case had we been able to increase the volatile acids in the identical form in which they occur in butter. Presumably free fatty acids would be more irritating than when combined, and a triglyceride composed entirely of short chain acids (tributyrin) might well be more irritating than triglycerides such as exist in butter where long and short chains occur in the same molecule.

The results indicate that volatile fatty acids, even in quantities well above those present in butter, are not to be feared. Table VIII shows that fat retention in these experiments remained within the normal limits, indicating that the volatile acids are well absorbed. This is further attested to by the low Reichert-Meissl number of the stool fat in the tributyrin periods, as contrasted with the fat of the diet. The

*Personal observations indicate that the bubbling which occurs when butter is so heated is due to the escape of steam rather than of volatile fatty acids. The heating procedure recommended is quite ineffectual in reducing the Reichert-Meissl number of butter: a lot so heated had an R.M. number of 31 after heating as compared with 33 before heating. This result is not surprising when one stops to consider that the volatile acids in butter are not free but combined as triglycerides which have high boiling points.

TABLE VIII
INFLUENCE OF VOLATILE FATTY ACIDS ON FAT RETENTION

FEEDING	PERIOD	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	INGESTED FAT			FECAL FAT				FAT RETENTION	
					QUAN- TITY GM./ DAY	RICH EX- TRACT NUMBER	QUAN- TITY GM./ DAY	PARTITION			RICH EX- TRACT NUMBER	OIL/ DAY	% OF INTAKE RE- TAINED
								% N F	% P F.A.	% SOAP			
Free volatile fatty acids added to butter	H-t	4½	5.67	6	23.37	53.1	3.52	6.6	14.6	78.9		19.85	84.9
	H-t	5	6.09	6	38.60	53.1	3.04	8.8	39.5	51.7		29.56	90.7
Tributyrin added to butter	W-d	9½	7.80	6	37.00	58.0	3.67	8.4	20.8	70.8	9.0	33.33	80.1
	K. J-n	5½	6.90	6	27.00	58.0	2.70	7.8	12.3	80.4	3.6	24.90	90.2
Control observations on butter alone	Average of 3½ experiments	4½	5.49	5½	25.09	31.4	2.89	9.5	18.1	72.4	1.7	23.10	88.9

Average of four experiments.

R M value of the stool fat in these experiments is not far above that in the control periods and is much less than may occur in cases of diarrhea. These facts are in harmony with the view that the volatile fatty acids of the stool are derived chiefly from the carbohydrate rather than the fat of the diet.

B The Influence of Length of the Carbon Chain—As far as we are aware, this question has not been studied in man, and only a few observations have been made in animals. Among the saturated straight chain fatty acids it appears that absorption falls off to some extent when the chain becomes as long as 16 carbon atoms (palmitic) and even more so with the 18 carbon (stearic) acid. In dogs Arnschink⁴⁶ found that tristearin was only from 9 to 14 per cent absorbed, whereas Lyman⁴⁷ observed that in the dog tripalmitin was only slightly less well absorbed than was lard. Levites,⁴⁸ using dogs, compared the absorption of free palmitic and stearic acids and their sodium soaps, palmitic acid was absorbed to the extent of 63 to 78 per cent, whereas stearic acid was absorbed only 19 to 35 per cent. The difference was also present when the sodium soaps were compared, though it was less marked. Frank⁴⁹ and Muller and Mutschhauser,⁵⁰ working with dogs, found that ethyl palmitate was better absorbed than ethyl stearate, and in this laboratory, Cox,⁵¹ working with white rats, found that the 12 carbon ethyl laurate was very completely absorbed in contrast to ethyl stearate.

Our studies in children were made on two almost completely saturated fat mixtures. (1) cocoanut oil (iodine number, 8) which contains a considerable proportion of acids with only 12 and 14 carbon atoms and has a mean molecular weight of 218, and (2) a mixture of tripalmitin and tristearin (approximately 2:1) which had an iodine number of 2 and a mean molecular weight of 278. Table IX shows that the material containing the shorter chain fatty acids is more completely absorbed.

C Relation of Iodine Value and Melting Point to Fat Absorption—A number of observations in the literature indicate that unsaturated fats are more readily absorbed. In 1889 Arnschink⁴⁶ had shown that dogs absorb olive oil better than they do tristearin. Munk and Rosenstein⁵² in 1891 in a patient with a chyle fistula noted that olive oil was better absorbed than other more saturated fats which they used. Schabad and Soroschowitz⁵³ in 1911 observed in infants an improved retention of fat when olive oil was added to the food, and, more recently, Frontali⁹ found that the substitution of olive oil for butter in the Czerny-Kleinschmidt butter-flour mixture increased fat retention. More impressive evidence upon this point can be obtained from the

TABLE IX
INFLUENCE OF LENGTH OF FATTY ACID CHAIN UPON FAT RETENTION

FAT FED	PERIOD	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	INGESTED FAT		FECAL FAT					FAT RETENTION	
					QUANTITY GM/DAY	MEAN MOLECU- LAR WEIGHT	GM/DAY as fed	PARTITION			GM/DAY	% OF INTAKE RE- TAINED	
								% N F	% F P A	% SOAP			
Coconut oil	K-n 3	1½	5.13	10	19.58		3.87	4.3	30.5	65.2	16.01	80.5	
	S-1 1	0½	6.42	6	30.80	218	1.75	7.9	36.4	56.4	29.05	94.3	
	W-3 5	9½	3.00	5	33.40		2.88	4.2	30.3	65.6	30.52	91.4	
	Average	7	6.52	7	28.03		2.53	5.2	32.4	62.4	25.19	88.7	
							9.35	5.5	33.7	60.3	14.89	61.4	
Tripalmitin-tri- stearin	J J-n 2	6½	3.00	3	37.40	373	1.43	17.8	32.0	50.2	22.97	61.5	
	K J-n 13	0½	7.27	6	30.00		11.52	5.5	43.9	51.3	18.48	61.6	
	Average	7½	6.94	5	30.55		11.77	9.9	36.0	54.1	18.78	61.5	

data of Langworthy and his associates,⁵⁴ who studied a large series of natural fats in adults. In Chart 2 we have plotted their average retention figures for various fats having a mean molecular weight above 270 against the iodine value of the fat*. Similar data of our own in infants are plotted in the same graph. The two sets of data are in good agreement and illustrate the relation between retention and unsaturated linkages in a fat.

It is easy to suppose that greater ease of absorption of short chain fats and unsaturated fats is due to a property they possess in common—a low melting point. Indeed in the past the melting point has been generally regarded as the factor limiting absorption. It was originally maintained⁵⁵ that fats melting above the body temperature were not

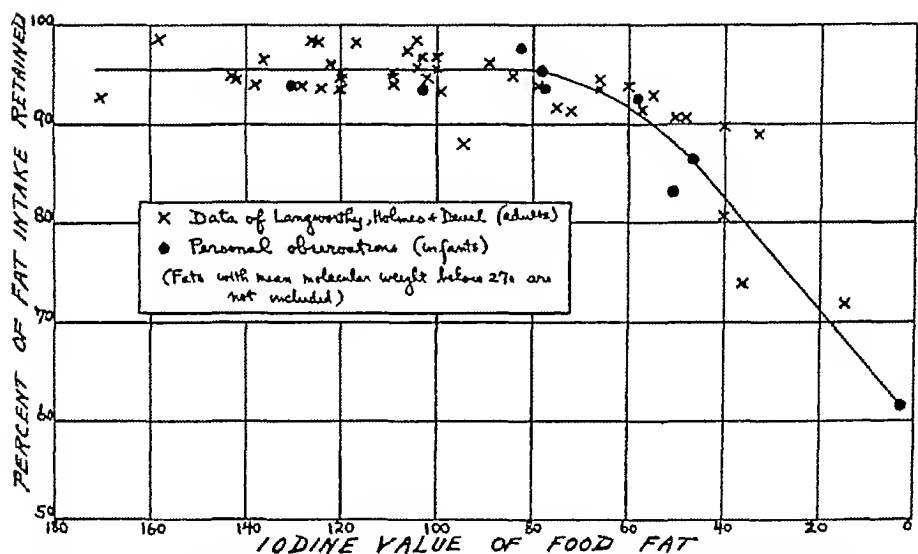


Chart 2—Relation between iodine value of food fat and fat retention (average figures)

readily absorbed, but this was subsequently found not to be strictly true. Langworthy and his associates⁵⁴ in their study of hydrogenated oils noted impaired retention only when the melting point rose above 45° or 50° C. From data hitherto available it has not been possible to decide whether it was the lower melting point or the accompanying difference in chemical constitution which favored absorption, but we now wish to present evidence which indicates that it is the chemical difference rather than the difference in melting point which is significant.

In the course of hydrogenation of highly unsaturated fats, glycerides of elaidic acid are formed which, though isomeric with those of oleic

*Values for constants of the fats they used were not given by Langworthy. We have therefore used values taken from the literature and have included only fats for which the constants are reasonably well known.

acid and containing likewise one double bond, nevertheless melt at a comparatively high temperature. By using partially hydrogenated corn oil,* on the one hand, and a 2:1 mixture of tripalmitin and tristearin, on the other, we have been able to compare two fats of practically identical melting point which differed widely in their content of unsaturated fatty acid. The difference in retention is shown in Table X. It is apparent that the presence of double bonds ensures good absorption† regardless of the high melting point.

D *Relative Significance of the Total Unsaturation (Iodine Value) and the Percentage of Unsaturated Fatty Acids*—It seemed of interest to determine whether absorption is determined by the total number of double bonds in the fat (iodine value) or by the percentage of fatty acids which contain one or more double bonds. In order to test this point we compared two fats with an identical iodine value, one consisting almost entirely of a one double bond unsaturated fat (a very pure olein‡) and the other a mixture containing more highly unsaturated fatty acids and saturated fatty acids (made by mixing corn oil and butter). If the determining factor were the percentage of fatty acids containing one or more double bonds, instead of the iodine value, one would expect the pure olein to be better absorbed than the corn oil butter fat mixture. The data obtained indicate that this is the case (Table XI).

Neglect of this possibility has led at least one set of imitators of breast milk fat into error. Gerstenberger and Ruh,⁴⁴ in their preparation known as "S. M. A.," chose to imitate the iodine value of breast milk fat (which is largely due to the one double bond olein) by a mixture containing highly unsaturated fatty acids (from cod liver oil) and saturated fatty acids (obtained from tallow). They apparently overlooked the fact that such a mixture as theirs contains (according to our measurements) between 10 and 15 per cent more of the less readily absorbed saturated fatty acids than does average breast milk fat. We believe that this fact explains in part our findings on the retention of S. M. A. fat, which are presented in another section.

E *The Retention of Certain Odd Carbon Fats*—Since our studies on the utilization of certain odd carbon fats by infants and the methods of preparation of these materials are presented in more detail elsewhere⁴⁵

This material, known as "Argo," was supplied by the courtesy of the Corn Products Refining Company.

†It may be noted that the retention figures on hydrogenated corn oil (83 per cent) are slightly lower than what we have usually found (from 26 to 90 per cent) on olein containing fats of similar iodine number but of far lower melting point. It is possible that the higher mean molecular weight of this preparation will account for this slightly poorer retention.

‡This material consisted largely of triolein, but a considerable amount of mono-glyceride and diglyceride was also present.

TABLE X
RELATIVE IMPORTANCE OF IODINE VALUE AND MELTING POINT OF A FAT IN DETERMINING FAT RETENTION

FAT FED										FECAL FAT					FAT RETENTION	
	MELT- ING POINT	IODINE VALUE	MEAN MOLE- ULAR WEIGHT	PERIOD	AGE (MO)	WEIGHT (KG)	LENGTH OF PERIOD (DAYS)	FAT INTAKE GM / DAY	PARTITION				GM / DAY	% OF INTAKE RE- TAINED		
									GM / DAY	% N F	% F F A	% SOAP				
Partially hydro- genated corn oil (Argo)	50° C	50.2	283	J J—n 1	5½	7.75	6	37.20	6.90	11.8	22.8	65.4	30.30	81.5		
				K J—n* 12	6	7.10	6	28.60	4.43	11.8	15.9	72.3	24.17	84.5		
				Average	6	7.43	6	32.90	5.67	11.8	19.4	68.8	27.23	83.0		
Tripalmitin—tri- stearin (21)	53° C	2.4	278	H—t 5	3½	5.55	5	24.25	9.36	6.5	32.7	60.8	14.89	61.4		
				J J—n 2	6½	8.00	3	37.40	14.43	17.8	32.0	50.2	22.97	61.5		
				K J—n 13	6½	7.27	6	30.00	11.52	5.5	43.2	51.3	18.48	61.6		
				Average	5½	6.94	4¾	30.55	11.77	9.9	36.0	54.1	18.78	61.5		

*This infant had a slight coryza for part of the period but it did not seem to affect digestion or gain in weight.

TABLE XI
RELATIVE SIGNIFICANCE OF THE TOTAL UNSATURATION (IODINE VALUE) AND THE PERCENTAGE OF UNSATURATED FATTY ACIDS

FAT FED				PERIOD	AGE (MO)	WEIGHT (KG)	LENGTH OF PERIOD (DAYS)	FAT INTAKE GR/DAY	FECAL FAT				FAT RETENTION		COMMENTS	
IODINE VALUE OF FATTY ACIDS	SCN VALUE OF FATTY ACIDS	PERCENTAGE OF UNSATURATED FATTY ACIDS	OL/DAY						PARTITION			LOOKING VALUE OF FATTY ACIDS	GR/DAY	% OF FAT INTAKE RETAINED		
									% F A	% S A	% SOAP					
Corn oil— butter mixture	87.3	5.3	58.4	J S—h	3	4.00	6	19.23	4.56	34.0	13.6	52.4	52.7	14.67	73.3	Twin
				W S—h	3	2.70	6	18.98	3.46	24.7	20.0	55.3	67.1	15.52	81.3	Twin
				H—r	6	4.1	6	31.80	1.23	31.8	37.3	40.9	49.5	20.68	94.4	Aural discharge, Di
				K, J—n	17	7.1	3	37.50	3.63	31.3	39.8	38.4	48.5	23.87	86.8	gestion O K.
				Average		4.1	5.13	5.1	21.33	3.55	25.6	37.7	46.7	53.7	18.66	84.3
Pure olein	89.9	86.3	96.1	J S—h	4	4.40	6	24.00	2.66	53.0	37.1	10.9	73.8	31.34	88.9	Twin
				W S—h	4	4.30	6	23.75	5.04	41.4	46.3	12.3	82.5	18.71	78.8	Twin. Otitis and loose stools developed at end of period.
				H—r	7	5.15	5	23.99	0.77	37.3	27.2	45.0	60.0	23.32	96.3	Aural discharge part of the time. Di
				K, J—n	13	7	3	29.10	0.51	47.2	23.2	29.6	63.5	27.59	98.2	gestion O K.
				Average		4.1	5.41	5	24.36	2.25	43.3	31.0	26.7	71.3	23.72	90.7

they will only be summarized here. Briefly, we found that the glyceride of tridecyllic acid (C_{13}), in contrast to the findings of Verkade⁵⁷ on adults, was toxic although fairly well absorbed (55.5 per cent of the intake). The ethyl ester of margaric acid (C_{17}) was not toxic, but was absorbed to the extent of only 25 to 30 per cent of the intake (Table XII). A 1:4 mixture of the glycerides of pentadecyllic and margaric acids (C_{15} and C_{17}) was well tolerated and gave rise to no toxic symptoms when the intake was kept at 4 per cent. When this material was fed in the form of ketogenic diet, the feeding was not well taken, but even so 73.3 per cent of the intake was retained.

On this diet ketone bodies made their appearance just as would have been anticipated with even carbon fats. The possibility could not be excluded that the ketone bodies were formed from the patient's body fat rather than from the ingested fat although the latter seemed the more probable explanation and was in harmony with the observations of Verkade who found evidence for both beta-oxidation and omega-oxidation in the case of his odd carbon fats. From these few experiments one cannot draw accurate deductions as to the relative ease of absorption of odd and even carbon fats. It may be that, other factors being equal, the odd carbon fats are as well absorbed. The somewhat impaired retention noted with the odd carbon glycerides may well have been due to their more or less toxic action. With the ethyl esters of margaric acid we observed poorer retention than with the ethyl esters of butter (see Section H), but this would be expected since the odd carbon material had a higher mean molecular weight and contained no unsaturated linkages.

F. Observations on Feeding Split Fat—Poor fat retention and the presence of much unsplit fat in the feces is found in diarrheal states and in conditions with a deficiency of the external secretion of the pancreas. Lack of pancreatic lipase, in the latter instance, and inadequate time for it to act, in the former case, would explain the poor fat splitting, and it seemed probable that inadequate fat splitting was the cause of the poor absorption. These considerations led us to investigate the practicability of feeding split fat, an undertaking which promised success in view of the encouraging studies of Levites⁴⁸ on dogs. Levites found that free palmitic and stearic acid were distinctly better retained than their triglycerides, still better results were obtained with the sodium soaps, results which were quite comparable to those obtained with the readily absorbable fats. Aside from the precaution that the soap containing diets had to be made palatable, he noted no difficulties and no untoward results.

TABLE XII
OBSERVATIONS ON THE RETENTION OF CERTAIN ODD CARBON FATS

FAT FED	PERIOD	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	FAT INTAKE GM/DAY	FEDAL FAT				FAT RETENTION		ACETONE IN URINE	COMMENTS	
						GM/DAY	PARTITION			GM/DAY	% OF INTAKE			
							% C ₁₆	% C ₁₇	% C ₁₈					
Glyceride of C ₁₈	II-r	4	3½	4	10.2	8.56	22.8	27.6	49.6	10.60	85.5		Patient did not thrive on this feeding Stools loose vomited some. No gain in weight	
Glycerides of C ₁₆ and C ₁₇ (1:4)	II-k	7	8	7	38.80	10.23	28.2		71.8	28.07	73.2	+++	Thrived fairly well. Some refusal of food.*	
	McK-a	7	10	3	38.00	28.60	35.7	2.7	41.6	9.40	34.8	0	Rapid gain in weight following high ethyl ester period.	
Ethyl esters of C ₁₆	McK-a	8	10	8	40.00	28.48	14.7	29.3	47.4	11.53	28.8	0	Still gaining weight rapidly	
	McK-a	6	9½	3	95.00	71.00	65.7	2.6	9.0	24.90	26.0	+to++	Loading weight after start of high fat diet†	

*ketogenic diet, Woodruff ratio—0.5.

†ketogenic diet, Woodruff ratio—3.2.

In all we performed three experiments with split fat. In the first one, a mixture of palmitic and stearic acids* (approximately 2:1) was substituted for the milk fat. The material was homogenized without difficulty, but upon autoclaving, coagulation of the milk occurred so that sieving was necessary before it could be fed. Within a few hours after the experiment was started, the child developed diarrhea, which by the third day had become so severe that it was necessary to terminate the experiment, whereupon the diarrhea promptly subsided.

The metabolism study, though less accurate than our other studies because of the shortness of the period (forty-eight hours), is rather illuminating. Fat retention, as might have been anticipated in view of the diarrhea, was poor, being only 88 per cent. But altogether unexpected was the finding that a large part of the unabsorbed fatty acid appeared in the stool in the form of soap.

We did not feel justified in attempting further studies with free fatty acids in these quantities. Moreover, the above experiment indicated that little was to be expected from feeding palmitate and stearate in the form of soaps. However, inasmuch as Levites had reported better results with sodium oleate than with either free oleic acid or the soaps of palmitic or stearic acid, we undertook to feed two babies sodium oleate in place of the milk fat. The infants made no objection to the taste of these feedings, which were quite unpalatable to adults.† They continued to thrive and gain weight and their stools were only slightly softer than normal. However, they showed signs of thirst and a slight degree of fever (Charts 3 and 4) on an intake of water that had been previously sufficient, when allowed water ad libitum they consumed considerably more than before. Fat retention, as shown by the metabolism study, was fairly complete in both subjects. We have no explanation for the fact that a considerable amount of the stool fat in these periods consisted of neutral fat plus unsaponifiable matter.

On the whole we are not impressed with the feasibility of feeding split fat (Table XIII). The irritant properties of free fatty acids when all the fat is so supplied and the high water requirements when the fat is fed as sodium soap appear to be serious objections, at least as far as their use in diarrhea is concerned.

There is reason to believe, however, that smaller quantities of free fatty acids can be well tolerated—perhaps sufficient for the acidification of milk, it is rather remarkable in view of the great assortment of acids suggested for that purpose that the fatty acids should have

*This material was supplied through the courtesy of the Procter and Gamble Company.

†The aversion to the taste of soap seems to be acquired at a later period of life, for we have often seen young children eat considerable quantities of toilet soap with apparent pleasure.

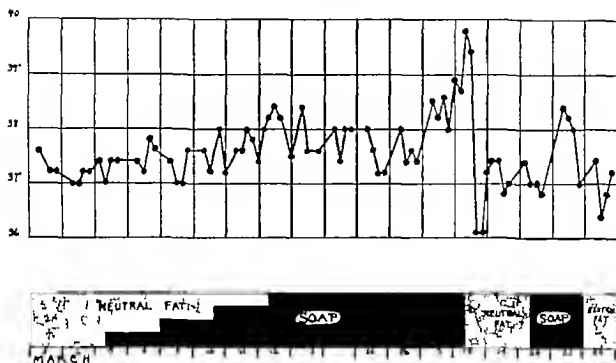


Chart 3.—Twin J S-h.

been overlooked. Some years ago von Mering⁵⁸ recommended the use of a mixture of olive oil plus 6 per cent free oleic acid (lipanin) and subsequent reports⁵⁹ in the German pediatric literature indicate that this was well tolerated.

G *The Utilization of Ethyl Esters*—As far as we are aware, ethyl esters have been studied only in animals. A number of balance experiments are on record. Frank⁴⁹ in 1898 fed ethyl palmitate and ethyl stearate to dogs and observed retentions of 75 per cent and 12 per cent, respectively. He made the interesting observation that when

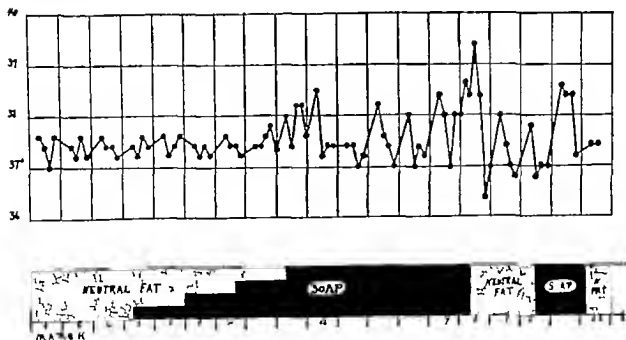


Chart 4.—Twin W S-h.

TABLE XIII
OBSERVATIONS ON FEEDING SPLIT FAT

FAT FED	PERIOD	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	FAT INTAKE GM / DAY	FECAL FAT				FAT RETENTION		COMMENTS
						GM / DAY	% N F	% F F A.	% SOA I	GM / DAY	% OF INTAKE RE- TAINED	
Free palmitic and stearic acid (2 I)	H-t	4	5.25	2	20.48	18.08	13.4	18.2	68.4	1.81	8.8	Severe diarrhea developed, necessitating stopping the experiment
	J S-h	8	6.70	5	26.46	5.82	46.4	14.7	38.9	20.64	78.0	"Soap fever" developed Weight stationary
Sodium oleate	W S-h	9	5.80	5	24.53	4.36	29.4	28.1	42.5	20.17	82.2	"Soap fever," weight sta- tionary
	Average	6	6.22	5	25.50	5.09	37.9	21.4	40.7	20.41	80.1	

TABLE XIV
THE RETENTION OF ESTERS

FAT FED	PERIOD	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	FAT INTAKE GM./KG.	FECAL FAT PARTITION				FAT RETENTION		ACETONE IN URINE
						GM./DAY	% N F	% F F A	% SOAP	GM./KG	% OF INTAKE RETAINED	
Ethyl esters of butter	W-d	3	5.70	8	35.10	19.43	47.3	23.6	29.4	15.68	44.7	
	M-r	3	4.95	8	26.00	15.76	34.0	24.6	41.4	10.24	39.4	
	M-r	4	5.40	6	31.00	16.74	38.9	18.1	43.0	14.26	46.0	
	McK-a	3	6.03	8	30.00	15.54	44.8	26.2	49.0	14.46	48.2	
	Average		5.52	7½	30.33	16.87	36.2	23.1	40.7	13.66	44.6	
Ethyl esters of butter fed at a high level	M-r	3	5.00	0	76.30	59.10	81.0	13.6	5.4	17.90	22.5	++
	McK-at	5	6.70	2	98.40	59.23	81.4	14.2	4.4	41.18	41.1	+++
	Average		5.85	4	84.85	59.60	81.2	13.9	4.9	29.19	33.3	

Observations on the retention of ethyl esters of margaric acid are included in Table XII

†Ketogenic diet, Woodyatt ratio—0.8 child lost weight.

‡Ketogenic diet, Woodyatt ratio—3.2 child lost weight. Since only a small fraction of the fat of these diets was absorbed it appears that ketogenesis took place at a far lower level of fat retention than would be expected on diets in which the fat was supplied as triglycerides.

ethyl esters were fed, triglycerides appeared in the chyle. Interest in the ethyl esters revived during the Great War with the possibility that they might be substituted for triglycerides as foods, the glycerin of natural fats being needed in the manufacture of munitions. Lyman⁴⁷ found that dogs absorbed only a trifle over 50 per cent of ethyl palmitate in contrast to tripalmitin and natural fats, which were more than 90 per cent absorbed. Muller and Murschhauser⁵⁰ working with dogs found that the ethyl esters of lard were less well absorbed (about 75 per cent) than the natural fat (91 per cent to 94 per cent). They studied the respiratory quotient and found evidence that the ethyl esters were burned, but they hesitated to recommend their complete substitution for natural fats because of their specific dynamic action. Cox⁵¹ recently fed ethyl esters to rats and found that growth curves on the esters of lard and of cocoanut oil were almost as good as those obtained with the natural fats. Difficulty of absorption was noted only with the longer chains (ethyl palmitate and ethyl stearate) when pure esters were fed.

Our own observations were made with the ethyl esters of butter fat. The three infants who were studied on this diet continued to thrive and gain weight normally throughout the period of this feeding (see page 429). Only when the stools were dried did it become apparent that a large part of the ester had not been utilized, for the stools contained large quantities of fat. Table XIV shows the very incomplete retention of the ethyl esters in contrast to control periods upon butter fat. The greater part of the difficulty appears to lie in the incomplete splitting of the ethyl esters.

These findings, together with the observation that ketosis occurs at a lower level of fat retention on ethyl ester diets, indicate that ethyl esters are certainly inferior to triglycerides as human foods and confirm the conclusion reached from animal studies.

H *A Comparison of Various Natural Fats and Proprietary Fat Mixtures Designed Especially for Infant Feeding*—In the course of our work we have studied seventeen different even carbon fats: four animal fats, six vegetable fats, and seven fat mixtures, five of which were from proprietary preparations.* Some of these experiments have been reported in the foregoing tables, the remainder are presented in Tables XV and XVI.

In Table XVII are summarized our experiments on different fats. The relation between retention and the composition of the fat is shown

*Several of these proprietary foods contain special features other than the fat mixture. These features we have not investigated; our studies being confined to the fat of the preparations. In some instances (S. M. A. Similac and Reolac) the fat was supplied us directly by the manufacturers. In others (Almata, New Zealand cream) it was extracted from the finished product by ether and rectified with petroleum ether.

in Table XVIII The fats are arranged in order of completeness of retention as nearly as this could be determined* from our data It is apparent that no single factor in the composition of the fat can be taken as an index of retention, the composition as a whole must be considered Fats with the highest percentage of unsaturated acids head the list, but among those with a lower proportion of unsaturated acids, it makes a considerable difference whether the saturated acids are predominantly short, medium, or long chain acids The saturated acids containing 14 carbon atoms or less make for good absorption, though they do not seem to be the equal of the unsaturated acids, for coconut oil is distinctly inferior to olive oil Palmitic acid is only slightly less desirable than the shorter ones, whereas stearic and the longer chain acids make for poor absorption In another section we have presented evidence that individual fatty acids are selectively absorbed when a mixed fat is fed On the assumption that the various acids are retained to the following extent

Unsaturated acids	98%
Short chain saturated acids	90%
Palmitic acid	88%
Stearic acid	60%
Saturated acids longer than stearic	40%

we have calculated the expected retention for the series of fats studied The retention so calculated is given in the last column of Table XVIII and is found to agree well with that actually observed The one exception is the palmitin stearin mixture, perhaps these difficultly absorbed fatty acids are more readily taken up in mixtures containing unsaturated or short chain acids than when they are present alone.

The composition as given in the table does not tell the whole story, for within the various groups of fatty acids which are tabulated the individual members doubtless show slight differences in ease of absorption. The data in the table illustrate the fallacy of imitating particular fats on the basis of determinations of a few selected constants, rather than on a complete analysis of the fatty acids. For example, in S. M. A. fat considerable pains were taken to duplicate the iodine value and saponification value believed to be characteristic of breast milk fat It appears, however, that the percentage of unsaturated acids fell well below the mark, a fact which would at once have become apparent if determinations of the thiocyanogen value had been

*In arranging these fats in Table XVIII we have not been guided exclusively by the average retention figure. Some of our subjects were better fat absorbers than others, and since it was not possible to make all comparisons on the same infants, we have taken into consideration the retention of a particular subject on the experimental fat diet as compared with a control period on butter fat.

TABLE XV
THE RETENTION OF VARIOUS ANIMAL AND VEGETABLE FATS

FAT FED	PERIOD	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	FAT INTAKE GM/DAY	FECAL FAT				FAT RETENTION	
						GM/DAY	PARTITION			GM/DAY	% OF INTAKE RETAINED
							% N F	% F F A	% SOAP		
Goat's milk fat	S-l	9½	6.60	5	32.80	1.66	9.7	27.6	62.5	30.14	91.9
	W-d	10	8.13	5	36.28	2.38	15.3	21.8	62.9	33.90	93.4
	Average	9½	7.37	5	34.54	2.02	12.5	24.8	62.7	32.02	92.7
Human body fat	K J-n	5	6.55	6	25.00	1.77	18.2	41.1	40.7	23.23	92.9
	F-r	5	5.13	6	18.85	1.16	20.5	18.9	60.6	17.69	93.8
	Average	5	5.84	6	21.93	1.47	19.4	30.0	50.6	20.46	93.1
Corn oil	H-t	5½	6.40	6	29.78	0.92	46.5	13.5	40.1	28.86	96.9
	G-n	3	3.97	6	21.99	0.87	23.0	32.9	44.1	21.11	96.0
	H-r	1	2.78	6	11.77	0.52	40.7	21.6	37.7	11.24	95.5
Olive oil	H-k	5½	4.40	6	22.65	0.76	39.4	35.2	25.4	21.89	96.7
	W S-h	5½	5.50	6	27.24	2.14	48.0	22.2	29.8	25.10	92.1
	Average	5½	4.16	6	20.91	1.07	37.8	28.0	34.2	19.84	95.1
Soy bean oil	W S-h	4	4.45	6	21.25	1.01	27.5	29.6	42.9	20.24	95.2
	H-r	3½	4.20	6	20.51	1.60	39.3	20.1	40.6	18.92	92.2
	Average	3½	4.33	6	20.88	1.30	33.4	24.9	41.7	19.58	93.7

TABLE XVI

THE RETENTION OF PROPRIETARY FAT MIXTURES DESIGNED FOR INFANT FEEDING

FAT FED	PERIOD	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	FAT INTAKE GM/DAY	FECAL FAT				FAT RETENTION	
						GM/DAY	PARTITION			GM/DAY	% OF INTAKE RETAINED
							% N F	% F P A	% SOAP		
S. M. 1 fat	K. J-n	1	4.20	6	22.20	8.03	20.5	26.9	62.6	14.17	63.8
	K. J-n	2	4.60	0	23.40	4.10	5.9	11.0	83.1	10.80	82.5
	K. J-n	15	7.85	6	31.20	4.34	6.2	12.8	80.1	20.86	86.1
	M-r	5	5.80	6	30.40	5.59	0.1	15.0	70.9	24.81	81.6
	M-r	6	6.15	6	31.70	3.65	17.3	74.0	88.8	28.15	88.8
	F-r	3	3.80	6	23.40	2.60	7.0	10.7	82.3	20.80	88.0
	S-l	4	6.65	6	29.70	3.11	8.3	24.0	67.7	26.59	89.5
	J J-n	4	8.64	6	36.90	3.68	8.9	26.5	64.6	30.22	89.7
	W-d	10	8.35	0	30.60	5.79	4.7	16.7	78.6	30.81	84.2
	Average (excluding period K. J-n 1)	6	6.48	6	30.29	4.10	7.5	16.8	76.0	26.19	86.3
Simlae fat	K. J-n	3	4.85	0	23.81	2.08	11.3	20.2	60.5	21.73	91.3
	M-r	7	6.40	6	29.80	2.30	10.7	15.4	73.1	27.00	92.2
	F-r	0	4.00	6	21.00	1.17	22.7	27.0	40.7	19.83	94.4
	Average	4	5.08	6	21.70	1.85	14.9	23.1	63.0	22.55	92.6
Reolae fat	K. J-n	6	5.75	6	20.10	1.68	0.1	10.8	71.1	23.48	93.5
	M-r	10	7.30	0	28.73	2.81	7.2	10.0	82.8	25.91	90.2
	F-r	8	4.55	6	19.91	1.57	9.0	12.4	78.6	17.64	91.8
	Average	5	5.57	5	24.34	2.00	8.4	14.1	77.5	22.54	91.5
Ultama fat	K. J-n	8	6.03	6	25.71	2.85	15.7	12.0	72.3	23.86	88.9
	M-r	12	7.75	6	28.30	1.96	20.8	11.9	67.1	20.34	98.1
	F-r	10	4.99	6	19.70	1.41	21.5	13.5	65.0	18.29	92.8
	Average	5	6.26	6	24.57	2.07	19.3	12.5	68.2	22.50	91.6
New Zealand cream	K. J-n	7	0.05	6	25.90	1.34	20.4	20.5	59.1	24.50	94.8
	M-r	11	7.50	6	29.31	2.24	12.6	11.0	76.4	27.07	92.4
	F-r	9	4.75	6	20.30	1.58	26.6	19.8	53.6	18.79	92.1
	Average	5	6.10	6	25.17	1.72	19.9	17.1	63.0	23.45	93.1
Butter controls	Average	1	5.55	6	24.18	1.93	14.1	14	71.3	22.25	92.0

* M. 1. fat started one day before. Refusal and failure to gain first three days.

† n average of butter fat periods on subjects K, J-n, M-r and F-r each subject being given equal weight.

SUMMARY OF EXPERIMENTS IN WHICH THE

FAT FED	NUMBER OF EXPERI- MENTS AVERAGED	TABLE NO	AGE (MO)	WEIGHT (KG)	LENGTH OF PERIOD (DAYS)	FAT INTAKE GM/DAY	DRIED STOOL	
							GM/DAY	% FAT IN
Olein	2	12*	6	6.53	4	26.05	4.49	14.2
Olive oil	4	16	3½	4.16	6	20.91	4.98	20.5
Soy bean oil	2	16	3½	4.33	6	20.88	5.22	25.4
Human body fat	2	16	5	5.84	6	21.93	7.34	20.0
Breast milk fat	7	3	5	6.12	6	24.89	7.57	23.8
New Zealand cream	3	17	5½	6.10	6	25.17	6.89	25.2
Goat's milk fat	2	16	9½	7.37	5	34.54	8.76	23.2
Similac	3	17	4½	5.08	6	24.70	7.26	25.6
Recolac	3	17	5½	5.87	5½	24.34	7.12	28.5
Almata	3	17	5½	6.26	6	24.57	6.53	31.1
Corn oil—butter	2	12*	6	6.40	4½	24.65	7.63	30.1
Butter	35	2	4½	5.49	5½	25.99	8.17	35.2
Cocoonut oil	3	10	7	6.52	7	28.03	10.29	26.9
S M A	8	17	6½	6.48	6	30.29	11.45	35.9
Argo	2	11	6	7.43	6	32.90	14.69	38.2
Tripalmitin tristearin	3	10	7½	6.94	5	30.55	21.36	55.2
Fat free	5	18	5½	5.96	4	1.06	10.62	4.8
High fat diets	Butter	5	18	7	5.96	3½	67.12	5.22
	Goat's milk fat	5	18	7	6.01	3½	65.87	4.74
	Human fat	2	18	8½	7.15	3	68.85	3.96
	Soy bean oil	2	18	7½	6.55	3	62.51	3.79
	Ethyl esters of butter	2	15	7½	5.85	4	84.85	69.28
	Ethyl esters of butter	4	15	5½	5.52	7½	30.53	23.38
Ethyl esters of C ₁₇	2	18	10	7.00	3	39.00	40.60	70.3
Sodium oleate	2	14	6	6.25	5	25.50	11.52	44.0
High Reichert Meissl fat	4	9	6½	6.62	5½	30.14	10.46	31.5
High ash butter	3	3	6½	6.37	6½	26.41	12.83	36.8
Low ash butter	2	3	3½	5.44	6½	27.56	5.51	26.5
Low ash breast milk fat	2	3	4	5.40	8	24.61	2.83	26.1

*Experiments on twins not included

†Based on two experiments only

‡Based on four experiments only

made Similarly, if the saturated esters from S M A fat had been fractionated, the relatively high proportion of stearic acid would have been discovered Failure to observe these precautions resulted in a fat mixture which was not only inferior to breast milk fat but was not even as well absorbed as the butter fat it was designed to replace

The other fat mixtures designed for infant feeding appear to have slight, if any, advantage over butter fat, with the possible exception of New Zealand cream, which gave figures a trifle higher than the others and which contains a higher proportion of unsaturated acids This fat, the chief ingredient of which is peanut oil, is unique in containing appreciable quantities of the 20 carbon arachidic and the 24-carbon lignoceric acids Although clinical experiences with peanut oil appear to have been favorable, evidence from experimental animals⁶⁰ suggests that these long chain acids may not be readily disposed

XVII

FAT AND OTHER FEATURES WERE VARIED

FECAL FAT							FAT RETENTION	
GM./DAY	PARTITION						GM./DAY	% OF INTAKE RETAINED
	GM. PER DAY			PER CENT				
	N F	F F A.	SOAP	N F	F F A.	SOAP		
0.64	0.22	0.17	0.25	37.5	25.2	37.5	25.41	07.5
1.07	0.48	0.20	0.35	37.8	28.0	34.2	10.84	0.1
1.80	0.46	0.31	0.54	38.4	24.9	41.7	19.68	03.7
1.47	0.28	0.48	0.72	19.4	80.0	50.6	20.46	03.4
1.85	0.33	0.59	1.03	13.1	33.9	5.9	23.04	02.4
1.72	0.89	0.28	1.12	19.9	17.1	03.0	23.45	03.1
1.02	0.26	0.40	1.27	12.5	24.8	62.7	32.02	02.7
1.85	0.25	0.40	1.10	14.0	23.1	62.0	22.85	01.6
2.00	0.15	0.26	1.57	8.4	14.1	77.5	22.34	01.8
2.07	0.39	0.23	1.43	19.3	12.5	63.2	22.50	01.0
2.46	0.53	0.96	0.95	21.8	38.6	69.6	21.78	00.6
2.88	0.25	0.54	2.09	0.5	13.1	72.4	23.10	88.0
2.84	0.14	0.90	1.60	5.2	32.4	02.4	20.19	88.7
4.10	0.29	0.68	3.13	7.2	16.8	76.0	26.10	90.5
5.67	0.02	1.14	3.66	11.8	19.4	68.6	27.23	63.0
11.77	1.27	4.23	6.23	9.9	66.0	54.1	18.78	61.7
0.51	0.07	0.06	0.37	16.2	12.5	71.4	0.55	51.7
3.01	0.46	0.25†	6.16†	14.6	9.3†	76.1†	64.11	95.5
2.43	0.29†	0.42†	1.53†	12.5†	16.2†	71.0†	63.44	96.3
2.49	0.89	2.11		16.0	84.0		66.36	96.4
1.96	0.85	1.09		46.2	56.8		60.53	96.9
55.66	45.19	7.76	2.75	61.3	13.9	4.9	29.10	33.3
16.67	6.21	3.89	6.76	36.2	23.1	40.7	16.66	44.6
28.54	7.14	8.70	12.70	25.0	80.6	44.5	10.40	25.3
5.09	1.69	1.05	2.05	87.0	21.4	40.7	20.41	80.1
3.28	0.25	0.70	2.28	7.8	21.8	70.5	26.91	89.0
4.74	0.29	1.12	3.29	0.7	25.0	68.3	21.66	81.7
1.46	0.17	0.66	0.62	11.3	48.0	40.8	25.10	94.8
0.71	0.12	0.82	0.27	17.7	43.8	33.6	23.91	97.1

of by the body and may accumulate in the liver a fact which leads one to question the advisability of giving a diet rich in peanut oil for a prolonged period of time

From the point of view of retention, none of the natural fats and fat mixtures studied yielded such high figures as did olive oil and soy bean oil. These figures were exceeded only in the two experiments in which pure olein was fed

We do not wish to lay too much emphasis on the order in which these fats have been placed in the table. Because of the large number of fats studied the number of observations on particular fats was often small, and it is not improbable that a larger series of experiments would shift the position of one or another of these fats to some extent. To extend our observations sufficiently to permit a rigorous statistical comparison seemed to us an unprofitable task for we felt that the data obtained had answered several questions. They showed with sufficient clearness that all fats were not alike that ease of absorption

TABLE XVIII

RELATION BETWEEN RETENTION AND COMPOSITION OF FAT

	FAT FED					PER CENT RETENTION	
	COMPONENT FATTY ACIDS (%)*						
	UN SATU RATED ACIDS	SATURATED ACIDS					
		SHORT CHAIN ACIDS	PALMITIC ACID	STEARIC ACID	LONGER CHAIN ACIDS	OB SERVED	CALCU LATED
Oleic	96	<1	2	1	<1	97.5	97.0
Olive oil	89	<1	8	3	<1	95.1	96.0
Soy bean oil	88	<1	7	5	<1	93.7	95.1
Human body fat	67	8	20	5	<1	93.4	93.5
Breast milk fat	55	6	29	10	<1	92.4	91.1
New Zealand cream	77	5	8	5	5	93.1	91.8
Goat's milk fat	36	34	19	11	<1	92.7	89.2
Similac	33	47	14	6	<1	92.6	90.5
Recolac	35	43	15	7	<1	91.8	90.4
Almata	52	26	12	10	<1	91.6	91.0
Corn oil—butter mix ture (1 1)	58	21	13	8	<1	90.6	91.7
Butter	26	42	20	12	<1	88.9	88.1
Cocoanut oil	8	81	9	2	<1	88.7	89.8
S. M. A	43	12	20	25	<1	86.3	85.5
Argo	54	1	8	37	<1	83.0	83.0
Palmitin stearin (2 1)	3	1	64	32	<1	61.5	79.3

*Approximate values compiled and computed from data in the literature

was dependent upon chemical composition, and that neither breast milk fat nor human body fat—though superior to butter—represented the ideal in this respect, for both were surpassed by several vegetable fats. The differences in retention which we had found with most of these fats were relatively small and for the normal subject could have but little practical significance. It seemed quite possible, however, that in subjects with difficulty in fat assimilation, the small observed differences might prove to be large ones of considerable significance. Since we were primarily interested in these abnormal subjects, we have continued our metabolism studies upon them, attempting to confirm the differences observed in the normal subject and to see if these were accentuated. The results of this study are presented in another paper.

IV CERTAIN PROBLEMS RELATING TO FAT ABSORPTION

A. Influence of the Quantity of Ingested Fat—Observations on Fat-Free and High Fat Diets—For various reasons we undertook studies in which the quantity of ingested fat was varied as widely as possible. We were interested in any clinical phenomena that might appear, in the effect of fat intake upon fat retention, and, in addition, we hoped by means of fat-free diets to obtain qualitative and quantitative information as to endogenous fat excretion in infants. This last subject has been extensively studied in animals, notably by Sperry,⁶¹ but few observations have been made in man.

Our fat free diets were not completely devoid of fat, but the intake was reduced to approximately 1 gm per day. They were prepared from powdered skimmed milk with added sugar. The caloric intake in these periods was reduced, but in order to supply maintenance requirements it was necessary to make some increase in the quantity of protein and carbohydrate ingested. On this diet two very definite effects were noted. Within twenty-four hours all three infants developed loose, mushy, fermentative stools. The character of the stools tended to improve on subsequent days but did not return to normal until the termination of the experimental diet. This change in the character of the stools has been noted by others,⁴² but it is by no means clear whether it is due to absolute reduction of fat or to relative excess of carbohydrate in the diet.

The second phenomenon occurred in only one of the babies (H—t). This infant, shortly after the fat free diet was instituted, developed eczema and spasmodic bronchitis. We believed this to be a mere coincidence until it was found that these symptoms cleared up when fat was added to the diet and recurred when it was again withdrawn. A further report of this case and a discussion of the relation between fat in the diet and allergic manifestations may be found in the report of Dr. M. I. Rubin.⁴³

The chemical data on these periods are given in Table XIX. It is apparent that the fecal fat drops to a very low level, averaging only 0.5 gm a day. The retention figure here has little significance, for it is probable that about four-fifths of the fecal fat consists of endogenous fat excreted into the intestine. Approximately 40 per cent of the fecal fat consisted of unsaponifiable material, having an iodine value of 66.5. The quantity of fecal fat observed under these conditions is somewhat larger than that reported by Birk⁴⁴ (from 0.17 to 0.28 gm. a day in infants) or by Parsons⁴⁵ (0.2 gm. a day in older children).

A number of our subjects were studied for short periods on ketogenic diets. All of these infants developed an abundance of ketone bodies in the urine, nor did we observe any differences in the behavior of particular fats with regard to ketogenesis if we exclude the periods on ethyl esters of butter which have been mentioned above (Table XIV). In collaboration with Dr. H. W. Josephs, studies were also made of the urobilin output in the stools; these are reported in detail elsewhere.⁴⁶ It was found that these ketogenic diets led to a definite increase in the stool urobilin, but differences in the behavior of particular fats were not encountered.

The determinations of the fat balance (Table XIX) show that the percentage retention is somewhat better than on the periods of nor-

TABLE XIV

FAT RETENTION ON FAT-FREE AND HIGH FAT DIETS

TYPE OF DIET	FAT FED	PERIOD	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	FAT INTAKE (GM./DAY)	PERCENT FAT				FAT RETENTION		COMMENTS
							GM./DAY	% N F	% F F A	% SOAP	GM./DAY	% INTAKE RETAINED	
Fat free	---	11-12	9	6.80	7	1.17	0.63	22.1	15.5	62.1	0.54	46.3	Developed eczema and asthma
		11-12	10	4.10	2	0.98	0.58	18.4	28	78.9	0.40	40.5	
		11-12	11	4.10	1	0.99	0.11	12.2	1.5	74.3	0.58	58.5	
		11-12	11	7.05	2	1.08	0.41	11.6	14.3	74.1	0.65	60.2	
	---	11-12	11	7.15	4	1.08	0.51	16.2	16.2	67.5	0.57	53.8	
		Average	5.5	7.96	4	1.06	0.51	16.2	12.5	71.4	0.55	51.7	
Butter	---	11-12	9	6.70	6	76.75	3.25	14.0	8.2	77.8	7.50	95.8	
		11-12	10	6.30	3	71.25	3.40	15.3	8.4	74.7	67.85	95.2	
		11-12	10	6.30	3	67.29	10.2	17.3	9.7	82.7	63.27	94.0	
		11-12	6	5.30	3	60.80	2.20	15.9	8.1	84.1	58.60	96.4	
	---	11-12	6	5.72	3	59.52	2.20	11.3	10.3	78.4	57.32	96.3	Discharge from ears
		Average	7	5.96	3.1	67.13	3.01	14.6	9.3*	79.1*	64.11	95.2	
High fat (low ash) diet	---	11-12	6	5.75	3	63.92	2.14	10.8	18.1	71.1	61.78	96.7	Otitis, discharging
		11-12	10	7.78	3	67.37	2.61	12.8	20.2	67.1	64.76	96.1	
		11-12	6	5.00	3	56.40	2.71	13.1	16.4	70.6	53.69	95.2	
		11-12	8	5.40	3	55.77	1.65	13.3	18.1	68.8	54.12	97.0	Discharge from ears
	---	11-12	10	8.10	4	55.89	3.06				82.83	96.4	
		Average	7	6.01	3.1	65.57	2.43	12.5†	15.7†	71.9†	63.44	96.3	
Human body fat	---	11-12	8	7.10	3	67.50	1.81	17.4		82.6	65.69	97.3	Otitis, discharging
		11-12	8	7.20	3	70.20	3.17	14.6		85.4	67.03	95.5	
		11-12	8	7.15	3	68.85	2.49	16.0		84.0	66.36	96.4	
		11-12	6	6.50	3	63.70	2.52	45.4		54.6	61.24	96.0	
	---	11-12	10	6.60	3	61.26	1.34	41.0		59.0	59.92	97.8	
		Average	7.1	6.55	3	63.51	1.93	43.2		56.8	60.58	96.9	
Olive oil	---	11-12	8	7.54	2	70.04	1.99	48.5		51.5	68.06	97.2	
		11-12	13	7.57	3	57.12	2.62	60.2		39.8	54.60	95.6	

* Average of two experiments only
† Average of four experiments only

mal fat intake, moreover, the differences in the fats are practically wiped out. We are inclined to believe that the improved retention on the high fat diets to the comparisons of high and normal butter fat rations in which the mineral intakes were similar in the percentage retention.* This question is taken up in the following section.

B The Relation Between the Dried Weight of the Fat, and Fat Absorption—In the foregoing discussion we have gone on the assumption that, barring constipation, the most significant measure of fat absorption is the percentage of the fat intake retained. In this we have followed the practice of workers in the field. The correctness of this point has, however, been challenged particularly by H. S. Hutchison. His views have met with some acceptance, a defense of which would seem to be in order.

Hutchison observed in normal subjects and individuals in various pathologic states as well, that the percentage of fat in the feces was singularly constant, being approximately one-third of the fecal weight. Despite the fact that quite different percentages had been found in the feces of dogs and rats, he concluded that the percentage of fat was physiologic for human feces and that the question of the possible functions of fecal fat was of minor importance. He conceded that a decreased absorptive ability of the intestine to absorb fat would result in an increased percentage of fat in the feces, an increased quantity of fecal fat, and hence a decreased percentage retention; but he maintained that the converse was true: an increased quantity of fecal fat and consequent low percentage retention did not necessarily imply difficulty in absorption.

He described a state, due to atony of the bowel or to other factors related to fat absorption, in which the pathologic process increased the bulk of the feces, fat would then be diverted to the feces in order to maintain the physiologic percentage, even though the intestine had in no way lost its ability to absorb fat. In such a case the percentage retention would be low although the ability of the intestine to absorb fat had not suffered. The clue to this situation would be the fact that the percentage of fat in the stool failed to increase. From these premises it follows that the percentage of fat in the feces is a more valuable criterion of absorption than the percentage retention.

A second point made by Hutchison to show that the percentage retention is not the significant criterion of absorption concerns

In a preliminary communication (Proc. Third Internat. Paediat. C. conf., 1933) we stated our impression that the percentage retention of fat to diminish as the quantity of ingested fat was increased. Further studies, particularly those on high fat diets, have failed to sustain this view which we now retract.

TABLE XIV

FAT RETENTION ON FAT TYPE AND HIGH FAT DIETS

TYPE OF DIET	FAT FED	PERIOD (DAYS)	WGT (KG)	AGE (MO)	FAT INTAKE GM/DAY	FECAL FAT			FAT RETENTION		COMMENTS
						% V F	% P F	% A	GM/DAY	% INTAKE RETAINED	
Fat free	---	1-1	6.80	5½	1.17	2.2	15.5	62.1	0.54	46.3	Developed eczema and asthma
		1-2	4.10	6	0.98	18.4	2.8	78.9	0.40	40.5	
		1-3	4.10	6½	0.99	12.2	13.5	74.3	0.58	58.5	
		1-4	7.05	11	1.08	11.6	11.3	74.1	0.65	60.2	
		1-5	7.15	11	1.08	16.2	16.2	67.5	0.57	52.8	
	Butter	Average	5.96	5½	1.06	16.2	12.5	71.4	0.55	51.7	
		1-6	6.30	9	76.75	14.0	8.2	77.8	71.50	95.8	
		1-7	6.30	7	71.25	16.3	8.7	81.7	67.85	95.2	
		1-8	6.20	7	67.29	17.3	8.2	82.7	63.27	94.0	
		1-9	5.10	6½	60.80	16.9	8.1	84.1	59.60	96.4	
High fat (low ash) diet	Goat's milk fat	1-10	5.72	6	59.52	11.3	10.3	78.4	57.32	96.3	Discharge from ears
		Average	5.96	7	67.12	14.8	9.3*	78.1*	64.11	95.6	
		1-11	7.75	8½	67.92	10.8	18.1	71.1	61.78	96.7	Obtuse, discharging
		1-12	5.78	6½	67.37	12.8	20.2	67.1	64.76	96.1	
		1-13	5.00	6	50.40	13.1	16.4	70.6	53.69	95.2	
	Human body fat	1-14	5.40	5½	55.77	13.3	18.1	68.8	54.12	97.0	Discharge from ears
		1-15	8.10	10	85.89	3.06			92.83	96.4	
		Average	6.01	7	65.87	12.5†	16.7†	71.0†	63.44	96.3	
		1-16	7.10	8½	67.50	17.4		82.6	65.69	97.3	Obtuse, discharging
		1-17	7.20	8½	70.20	14.6		85.4	67.03	95.5	
Soy bean oil	---	1-18	7.15	8½	68.55	16.0		84.0	66.56	96.4	
		1-19	6.50	7½	63.76	45.4		54.6	61.24	96.0	
		1-20	6.60	7½	61.26	41.0		59.0	59.92	97.8	
	Olive oil	Average	6.55	7½	62.51	43.2		56.8	60.58	96.9	
		1-21	7.54	8½	70.04	48.5		51.5	68.06	97.2	
		1-22	7.57	8½	57.12	60.2		39.8	54.60	95.6	

* Average of two experiments only
† Average of four experiments only

mal fat intake, moreover, the differences in the behavior of individual fats are practically wiped out. We are inclined to attribute this improved retention on the high fat diets to the lower mineral intake. Comparisons of high and normal butter fat periods made under conditions in which the mineral intakes were similar show little difference in the percentage retention.* This question is further discussed in the following section.

B The Relation Between the Dried Weight of the Feces, the Fecal Fat and Fat Absorption—In the foregoing discussions of our results, we have gone on the assumption that, barring conditions of low fat intake the most significant measure of fat absorption is the percentage of the fat intake retained. In this we have followed the majority of workers in the field. The correctness of this point of view has however been challenged, particularly by H. S. Hutchison⁶⁷ and, since his views have met with some acceptance a defense of our procedure would seem to be in order.

Hutchison observed in normal subjects and individuals in certain pathologic states as well, that the percentage of fat in the dried feces was singularly constant, being approximately one-third of the dried fecal weight. Despite the fact that quite different percentages of fat had been found in the feces of dogs and rats, he concluded that this percentage of fat was physiologic for human feces and raised the question of the possible functions of fecal fat. He conceded that impaired ability of the intestine to absorb fat would result in an increased percentage of fat in the feces, an increased quantity of fecal fat, and low percentage retention, but he maintained that the converse was not true, an increased quantity of fecal fat and consequent low percentage retention did not necessarily imply difficulty in absorption.

He described a state due to atony of the bowel or to other causes unrelated to fat absorption, in which the pathologic process led to increased bulk of the feces, fat would then be diverted to the feces in order to maintain the physiologic percentage even though the intestine had in no way lost its ability to absorb fat. In such a condition the percentage retention would be low although the ability of the intestine to absorb fat had not suffered; the clue to this situation would be given by the fact that the percentage of fat in the stool failed to increase. From these premises it follows that the percentage of fat in the feces is a more valuable criterion of absorption than the percentage retention.

A second point made by Hutchison to show that the percentage retention is not the significant criterion of absorption concerns the effect

In a preliminary communication (Proc. Third Internat. Paediat. Congress, Acta paediat. 14: 103, 1933) we stated our impression that the percentage absorption tended to diminish as the quantity of ingested fat was increased. Further observations particularly those on high fat diets, have failed to sustain this view which we now wish to retract.

of varying fat intake on fat retention * When he arranged his normal cases with liberal fat intake in order of the amount of fat ingested, it appeared that the fecal fat tended to remain constant regardless of the intake, whereas, if the percentage retention were the criterion of normal absorption, an increase in the intake would have been followed by an increase in the fecal fat

The points made by Hutchison are well taken, and his arguments appear to be convincing Nevertheless, we believe that his data are susceptible of a different interpretation, one which is in better harmony with our own results

In the first place, we believe that the available data, taken as a whole, do not justify the conclusion that the percentage of fecal fat tends to approach a physiologic norm Normal subjects under standard conditions show wide fluctuations in the percentage of fecal fat Even in Hutchison's own data such variations are found, in his normal infants the fecal fat varied between 20.7 per cent and 46.0 per cent, in his series of atrophic infants it varied between 23.4 per cent and 47.8 per cent, in subjects with tetany it was between 25.0 per cent and 51.0 per cent, and in those with uncomplicated rickets the extremes were 18.6 per cent and 52.9 per cent It thus appears that little reliance can be placed on the percentage of fat in the individual case, even if the average value were relatively constant Our own data (Table XVII) show, however, that the average value for the percentage of fecal fat is a constant only when butter is fed With the more readily absorbable fats it falls, and with the less readily assimilable fats it rises consistently Moreover, even on butter the percentage of fat in the feces fails to remain constant when significant changes are made in the composition of the diet We are inclined to attribute the constancy of the figure which Hutchison and others obtained to the fact that such observations were made under relatively constant conditions Hutchison made no attempt to test out his theory by producing independent variations in the fat and other constituents of the feces Such variations were produced in our experiments on fat-poor and on ketogenic diets Compared with normal periods, our fat-poor diets were richer in mineral, a factor which served to increase the bulk of the dried stool According to Hutchinson, this should have resulted in an increase in the fecal fat No such effect, however, was noted On the contrary the absolute amount of fat in the feces fell sharply, and the percentage of fecal fat fell well below what Hutchison regarded as characteristic for the human species Similar results were obtained by Holt and Fales⁶² with diets from which fat was less rigidly

*As we have pointed out above we agree with Hutchison that the retention percentage is an inaccurate guide to absorption when the fat intake is low

excluded their subjects receiving 50 to 70 gm of fat a day. In their experiments the total ash and the total solids of the stool were increased, and yet a sharp reduction occurred in the fecal fat. The absolute quantity was diminished, and the fecal fat constituted less than 10 per cent of the dried feces.

The converse experiment we carried out in the periods on ketogenic diets. In order to avoid overfeeding these infants the dietary constituents other than fat were reduced. The mineral content of the diet was somewhat less than half that of the normal periods, being comparable to that in our low ash diets. The total solids of the feces fell below normal and from Hutchison's thesis one would have expected a reduction in the fecal fat. However, no such reduction occurred. The percentage of fat in the feces increased to well above 50 per cent, and if we contrast these periods with our low ash periods in which butter was fed at the normal level, it appears that the absolute quantity of fecal fat was increased on the high fat diet. The percentage retention on the low ash periods is almost identical regardless of whether butter was fed at the normal level or at the ketogenic level. In the former case the average retention was 94.8 per cent whereas the average retention on high butter fat periods was 95.5 per cent. Unfortunately these experiments were not carried out on the same subjects. Possibly the slightly better retention percentage on the high fat periods was due to the fact that the infants were older. At least our data fail to confirm the view that the percentage of fat in the feces is constant for the species. The variations produced by diet suggest that the differences found between man, the dog, and the rat may also find their explanation in differences in diet. The retention percentage on the other hand appears to hold regardless of whether the fat intake is normal or high, although it falls on low fat diets because the endogenous fat excretion then comprises a large part of the fecal fat.

As regards Hutchison's second point, the relatively constant fecal fat in the presence of increasing fat intake, his data are unfortunately not given in sufficient detail to permit one to criticize them with certainty, but other explanations of this finding are possible. If his periods on high and low fat had been done in the same infants and within a short space of time failure to find an increase in the fecal fat on the high fat intake would have been much more significant. On the other hand, if (as may well be the case from the information furnished) the periods on lower fat intake were in young infants and those receiving from 30 to 40 gm a day were in older infants, the results may be explained on the basis that the older infants were more efficient fat absorbers. We ourselves have obtained evidence that fat

absorption is affected to some extent by age. In premature infants and in full-term twins fat absorption is very imperfect. To a less extent we have found this to be true of normal infants during the early weeks of life. In such subjects we have found the percentage of retention with butter fat to be nearer 80 per cent than 90 per cent, and the proportion of fat in the dried feces is nearer 1/2 than 1/3, hence even if we use Hutchison's measuring stick, these young infants appear to absorb fat imperfectly. Just when this state of affairs is outgrown is not easy to say. It may be that at the age of ten or twelve weeks fat absorption is as perfect as it ever will be, on the other hand, it may be that as the infant grows older his absorption improves—rapidly during the early weeks and more slowly thereafter, reaching the absolute maximum only in the latter part of the first year. This latter possibility would easily explain Hutchison's results. It is unfortunate that he did not record the ages of his patients. Our results, presented in Table XX, are compatible with the view that absorption is a function of age during the early months of life. In conclusion we feel that no adequate reason has, as yet, been adduced for abandoning the retention percentage as an index of fat absorption.

TABLE XX
RELATION BETWEEN AGE AND FAT RETENTION*

AGE GROUP	NUMBER OF OBSERVATIONS AVERAGED	PER CENT OF FAT IN DRIED FECES (AVERAGE)	PER CENT OF FAT INTAKE RETAINED (AVERAGE)
0-1 month	3	46.0	84.2
1-2 months	6	40.5	84.6
2-3 months	6	34.6	86.8
3-4 months	7	30.2	89.6
4-5 months	(1)	(44.0)	(84.8)
5-6 months	11	30.9	90.5
6-7 months	6	33.2	90.4
7-8 months	(1)	(36.6)	(91.7)
8-9 months	0	----	----
9-10 months	(1)	(38.3)	(87.3)

*This table includes all periods on normal full-term infants fed on butter fat skimmed cow's milk and some form of sugar. Periods on premature infants and twins are not included even if these infants had apparently overcome their early handicap for it seemed doubtful whether they could fairly be compared with full-term normal infants of the same age.

Although it is somewhat beside the present point, it may be well to point out that Hutchison's conclusions in regard to fat absorption in atrophic infants are no firmer than the premises on which they are based. Hutchison found, like others, that the percentage retention in these infants was somewhat low (average 76.5 per cent in twenty-two subjects) but he maintained that this was not due to impaired fat absorption. He attributed it to (1) a comparatively low fat intake and (2) an increase in the bulk of the feces, causing diversion of fat

to maintain the physiologic percentage in the feces. As we have pointed out, the latter contention does not seem to be well founded. As to the former, although we agree that a low fat diet will lead to a low percentage retention, we do not agree that such a slight reduction in the intake (e.g. to 17.6 gm a day) could diminish the percentage retention to the extent observed. It would probably require an intake as low as 5 gm a day to do this. In fact, Holt and Fales²² in four periods on normal subjects reported an average retention of 76.85 per cent with an average intake of 55 gm of fat a day. We have five periods on normal infants who received quantities of fat analogous to those given by Hutchison to his atrophic infants and who retained distinctly more of their fat. These subjects received 14.2 to 19.4 gm of fat a day (average 16.9 grams) and retained from 79.5 per cent to 90.9 per cent (average 85.1 per cent). It thus appears that the low fat retention in Hutchison's atrophic infants is not adequately explained by the low intake, making it necessary to return to the earlier view that these infants have a certain amount of difficulty in absorbing fat.

C The Selective Absorption of Individual Fatty Acids—In preceding sections we have shown that the character of the fatty acids which compose a particular fat determine the extent to which it is absorbed. However, it does not follow from this that there is selective absorption of individual fatty acids in a mixed fat. It is conceivable that the more readily absorbable fatty acids act as a leaven facilitating the absorption of all that are present. The question is largely one of academic interest, but, since it has been the subject of controversy²³ we shall present the evidence we have which bears upon it.

It has been generally found^{24, 25} that the fecal lipids are more saturated than those of the food. We ourselves have found this to be the case as the data in the accompanying graph (Chart 5) bear witness. This however does not necessarily mean selective absorption of unsaturated fatty acids for it is also possible (1) that unabsorbed unsaturated fatty acids may become hydrogenated during passage through the intestine and (2) that the lower iodine value of the fecal fat may be due to admixture with a more saturated endogenous fat excreted by the intestine. This latter possibility we have attempted to rule out by making a correction in the value of our fecal fat for endogenous fat excretion based on the assumption that the endogenous fat excretion is not materially different on diets containing fat than it was found to be on our fat free diets. By deducting from the total fecal fat this assumed value for endogenous fat excretion, we obtain a value for the unabsorbed food fat, thus we have plotted on the graph as the "corrected" fecal fat. An examination of Chart 5 shows that such a

correction fails to abolish the discrepancy between the iodine value of the food and of the fecal fat in the case of fats which contain an abundance of both saturated and unsaturated acids (in which selective absorption if it occurred should be conspicuous) On the other hand when we come to fats like olive oil that contain a very small percentage of saturated acids (and in which there would be little opportunity for selective absorption in any case) we find that the correction almost completely removes the discrepancy between the fecal and food fat. We can thus conclude that admixture with endogenous fat does not account for the lower iodine value of the fecal fat when mixed fats (saturated and unsaturated) are fed.

The possibility that unabsorbed unsaturated fatty acids may become saturated during passage through the intestine (as is known to be the

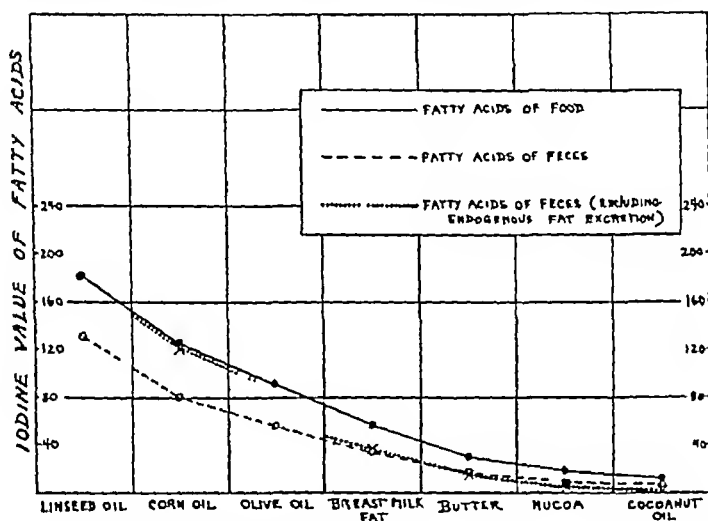


Chart 5—Comparison of iodine values of fatty acids of food and feces

case with sterols) was tested out in our experiments described in a foregoing section in which a comparison was made of a diet of pure olein with one of a mixture of corn oil and butter of identical iodine value. If saturation of double bonds occurred during passage through the intestine, there should be an identical lowering of the iodine value of the fecal fat in both sets of experiments. On the other hand, if there is no such saturation, the fecal residue on the olein diet should closely resemble olein in its iodine value, whereas on the corn oil-butter diet, in which selective absorption is possible, a considerable fall in the iodine value of the fecal fat might occur. The data in Table XI show the marked contrast between the two diets. On the pure olein diet the iodine value of the fecal lipids averages 71.2, being not far below that of the food fat, whereas in these same infants on

the corn oil butter mixture the iodine value of the fecal fat fell to an average value of 52.7, a drop twice as great as that in the olein diet. It is probable that had our olein been 100 per cent pure rather than only 95 per cent pure, the fall in the iodine value of the fecal lipids would have been even less. It thus appears that saturation during passage through the intestine will account for only a small part of the drop in iodine value of the fecal lipids and that selective absorption of individual fatty acids must occur in order to explain the values actually found.

By means of determinations of the iodine value and thiocyanogen value of the food and fecal fatty acids, using the formulas given by Jamieson,¹⁶ we have calculated the percentage of saturated acids of oleic acid, and of linoleic acid in the food and fecal fat, and from these figures we have obtained data as to the percentage absorption of these fatty acids in a mixed fat. The data are presented in Table XXI. The error in the method is such that significant figures for linoleic acid cannot be obtained when the amount ingested is less than 1 gm. a day as was the case with diets of breast milk fat and butter; these figures are therefore not included. However, in our periods in which corn oil was given, the feeding contained 5 gm. or more of linoleic acid a day, and the calculations assume some significance. Table XXI indicates that the oleic acid fraction regularly shows a better retention than the saturated acid fraction. In four of the five periods in which the retention of linoleic acid could be calculated with some degree of accuracy, the retention of linoleic exceeded slightly that of oleic acid; in one period the reverse was the case. We do not feel justified in concluding from this that linoleic is slightly better absorbed than oleic acid; more observations would be required to establish this point. The data suggest, however, that this may be the case.

D The Significance of the Fat Partition in the Feces—It has been the general practice to express this in percentages of neutral fat, free fatty acids, and soaps with the assumption—stated or implied—that variations encountered were due to differences in fat splitting. For example Holt, Courtney and Fales (quoted in Table I) found quite different percentages on diets of breast milk and cow's milk. Their findings are in general agreement with earlier authors and have since been confirmed by Harrison and Sheldon;¹⁷ a diet of breast milk gives rise to a higher percentage of neutral fat and free fatty acid in the feces, whereas on cow's milk a much larger proportion of soap is found. Our own experiments in which only the fat was varied show similar differences between breast milk fat and butter fat. However

TABLE XXI
RETENTION OF SATURATED AND UNSATURATED FATTY ACIDS WHEN MIXED
NATURAL FATS ARE FED

FAT FED	TUBES	INTAKE (GM/DAY)			OUTPUT IN FECES (GM/DAY)			RETENTION (GM/DAY)			RETENTION (% OF INTAKE)		
		LINOLIC ACID	OLEIC ACID	SATU- RATED ACIDS	LINOLIC ACID	OLEIC ACID	SATU- RATED ACIDS	LINOLIC ACID	OLEIC ACID	SATU- RATED ACIDS	LINOLIC ACID	OLEIC ACID	SATU- RATED ACIDS
Breast milk fat	G-n		9.90	6.75		0.13	0.71		9.77	6.01		98.7	90.4
	G-n		10.71	7.30		0.23	1.27		10.14	0.03		97.9	82.6
	K-n		11.60	10.02		1.02	2.39		13.67	7.63		93.1	76.1
	K-n		13.32	9.08		0.81	1.81		12.10	7.27		93.8	80.1
Butter fat	Average		12.16	8.29		0.55	1.66		11.60	6.74		95.9	82.0
	G-n		5.11	14.81		0.19	2.36		1.95	12.17		91.0	84.1
	G-n		5.17	14.84		0.27	2.91		5.18	11.90		95.0	80.2
	G-n		6.57	17.90		0.24	1.05		6.33	16.25		90.3	90.4
Low ash butter	G-n		6.57	17.90		0.23	1.05		6.34	16.25		90.5	90.8
	K-n		6.30	17.15		0.74	2.64		5.76	14.61		91.4	84.6
	K-n		6.65	18.10		1.17	3.06		5.48	15.04		82.4	83.1
	K-n		6.75	18.38		0.59	3.10		6.17	15.28		91.4	83.1
High ash butter	G-n		7.19	20.13		0.39	2.33		7.00	17.80		94.7	88.4
	K-n		6.04	18.00		0.06	0.91		6.58	17.19		99.1	85.0
	K-n		6.04	18.09		0.19	1.85		6.15	16.24		97.1	89.4
	K-n		7.47	20.31		0.14	1.73		7.03	18.01		94.1	91.5
High volatile acids added to butter	Average		6.5	17.80		0.12	2.20		6.12	15.69		93.6	87.3
	G-n		12.95	8.83		0.11	0.58		12.81	8.25		98.0	93.4
	K-n		15.35	10.46		0.05	0.87		15.30	9.89		99.7	94.6
	K-n		7.70	21.15		0.08	1.63		7.68	19.63		99.0	92.9
Olive oil	G-n		6.21	16.92		0.89	4.03		6.33	13.89		85.8	76.2
	K-n		5.91	16.04		0.27	3.01		6.04	13.93		95.4	82.2
	K-n		8.25	23.64		0.35	2.60		7.90	21.04		95.8	89.0
	K-n		17.99	3.03		0.24	0.58		17.75	2.45		98.7	80.9
Corn oil	G-n		13.61	3.93		0.24	0.48		13.33	3.45		97.9	89.0
	K-n		7.35	6.13		0.91	2.81		4.81	3.32		98.0	84.2
	K-n		7.25	6.05		0.66	1.56		6.01	4.49		88.4	74.2
	K-n		7.30	6.09		0.79	2.19		6.26	3.91		85.8	64.2
Corn oil and butter (mixture)	Average		8.13	6.95		0.43	0.72		7.90	0.23		94.8	89.6
	K-n		10.51	8.77		1.31	2.00		9.20	0.77		90.1	87.5
	K-n		7.37	7.86		0.20	1.36		7.19	6.50		97.5	83.4
	K-n		7.37	7.86		0.20	1.36		7.19	6.50		97.5	83.4

if we express the fecal lipids in absolute amounts rather than in percentages, a somewhat different impression is obtained

TABLE XXII

	PARTITION OF FECAL FAT					
	PERCENTAGE			GRAMS PER DAY		
	N F	F F A	SOAP	N F	F F A	SOAP
Average of 7 periods on breast milk fat	18.1	33.9	48.0	0.23	0.59	1.03
Average of 85 periods on butter fat	9.5	18.1	72.4	0.25	0.54	2.09

It then appears that the quantity of neutral fat and free fatty acid are approximately identical on the two diets and that the only difference is in the larger amount of soap in the stool on the diet of butter fat. If we examine our summarized experiments in Table XVII in which fat partition in the feces is expressed in absolute amounts as well as in percentages we find again that there is almost no variation in the daily excretion of neutral fat until we come to the very poorly absorbed fats like the palmitin stearin mixture and ethyl esters, and barring these there is no evidence of an inverse relation between retention and the amount of neutral fat in the stools. In other words *incomplete fat splitting does not seem to be a factor limiting absorption until we come to these very poorly absorbed fats*. This same point is illustrated in Chart 6 in which we have plotted data from individual experiments showing the relation between fat retention and the quantities of the various fecal lipids.

There does appear to be a slight inverse relation between the free fatty acid of the stool and fat retention, but there is a very striking inverse relation between retention and the quantity of soap in the feces. It is not clear what the factor is which limits absorption under these conditions; two explanations are possible. It may be that the difficulty is primarily with the absorption of soap. On the other hand, the fact that most of the unabsorbed fatty acid is found in the feces as soap may mean only that an excess of base has been available to neutralize unabsorbed fatty acid. Some observations made by Keller¹² suggest that the latter explanation is the correct one. He made analyses of the particular bases excreted as soap in the feces and found wide fluctuations: at times the alkali soaps were in excess and at other times the alkaline earth soaps were more abundant. These differences could not be attributed to the fat of the diet. Keller was led to the conclusion that the nature of the base combined as soap in the feces was dependent on the base available for excretion by this route at any particular time. This view was also supported by Folin and Wentworth.¹²

Inasmuch as the "neutral fat" fraction contained not only the neutral fat but also the unsaponifiable matter of the feces, we undertook to make some independent determinations of the unsaponifiable matter, as it seemed possible that the constant value of the neutral fat fraction might be due to the fact that this consisted largely of un-

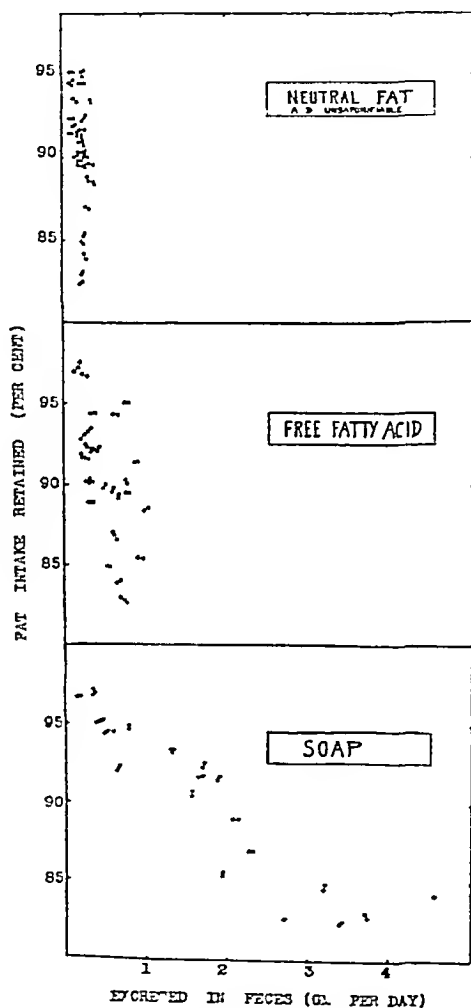


Chart 6—Relation between fat retention and the fat partition in the feces

saponifiable material. These determinations shown in Table XXIII indicate that the values obtained for unsaponifiable matter were, within the limits of error, identical with those we had obtained for the neutral fat fraction containing the unsaponifiable matter. In other words the feces contained no appreciable amount of neutral fat until we come to the poorly absorbed palmitin stearin mixture, in which

incomplete fat splitting makes its appearance. The somewhat higher values for "neutral fat" in the feces on diets of some of the vegetable oils can be attributed to the fact that these oils—notably corn oil—are richer in unsaponifiable matter, which is not completely absorbed. The iodine value of the unsaponifiable matter appears to be constant with the exception of the periods on vegetable oils during which it tends to be higher. This can be attributed to the fact that the unsaponifiable matter in these oils is highly unsaturated.

TABLE XXIII

OBSERVATIONS ON UNSAPONIFIABLE MATTER OF FECES

DIET		NUMBER OF EXPERIMENTS AVERAGED	UNSAPONIFIABLE MATTER OF FECES (GM./DAY)	IODINE VALUE OF UN SAPONIFIABLE MATTER
Olive oil		1	0.25	85.8
Corn oil and olive oil		1	0.42	
Corn oil		1	0.56	
Breast milk fat	Medium ash	4	0.22	61.6
	Low ash	2	0.13	68.6
Butter	Medium ash	16	0.27	64.8
	Low ash	2	0.15	63.2
Nucoa		1	0.25	—
Cocconut oil		2	0.20	68.8
Tripalmitin tristearin		1	0.22	—

In view of these findings it would seem to us desirable to abandon the conventional practice of expressing the fat partition in feces in percentages and to express this in absolute amounts. Erroneous impressions in regard to fat splitting are thus less likely to occur.

Conclusions

From the above studies we feel justified in drawing the following conclusions regarding the intestinal absorption of fat by infants:

1. The size of the fat particles is without influence on fat absorption.
2. Of other food constituents that might influence fat absorption, minerals alone appear to do so, exerting an unfavorable influence. This effect is probably due to the alkaline earths.
3. Volatile fatty acids in amounts considerably larger than those present in butter appear to be harmless.
4. In a mixed fat, absorption is favored by the presence of (a) fatty acids containing one or more unsaturated linkages and (b) fatty acids with relatively short carbon chains. It is impaired by the presence of long chain saturated fatty acids. Contrary to the general belief, the melting point of a fat is not per se the factor determining absorption.
5. Certain pure odd carbon fats, when pushed to ketogenic levels, will lead to the production of ketone bodies.

6 Split fat appears to be impractical for use in diarrhea, free fatty acids are irritating to the intestine, and soaps increase the water requirements

7 Ethyl esters are distinctly inferior to triglycerides. They appear to be split with difficulty and are retained only to a limited extent. When they are fed, ketone bodies make their appearance at an unusually low level of fat absorption.

8 A comparative study of various fats and fat mixtures indicates that those mixtures specially designed for infant feeding are no better absorbed than butter. Certain animal and vegetable fats are, however, distinctly better absorbed. The ease with which a particular fat is absorbed can be predicted, with considerable accuracy, from a knowledge of its composition.

9 Fat-poor diets tend to produce loose, fermentative stools, at times they appear to bring out allergic manifestations.

10 Fat absorption appears to be most satisfactorily measured by the percentage of ingested fat retained. This figure does not seem to be materially affected by increasing the quantity of fat in the diet, although it becomes inaccurate when the amount of ingested fat is very small since the fecal fat then consists largely of endogenous fat excretion.

11 To some extent fat absorption is affected by the age of the subject.

12 A constant relation between the total solids and the fat of the feces, such as has been claimed, does not appear to hold.

13 The claim that atrophic infants are able to absorb fat normally does not appear to be well founded.

14 Evidence is presented for the selective absorption of individual fatty acids in a mixed fat.

15 In normal subjects, fat is as a rule completely split in the intestine, the portion of the fecal fat usually reported as neutral fat actually consists of unsaponifiable material.

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STUDIES IN FAT METABOLISM

II FAT ABSORPTION IN PREMATURE INFANTS AND TWINS

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IN PART I of this study¹ the article dealing with normal infants, we reported certain differences in the absorption of particular fats which appeared to depend on the nature of the constituent fatty acids. From the point of view of absorption the most desirable fatty acids were found to be those containing unsaturated linkages and next to these, acids with relatively short carbon chains. It was not established that the presence of more than one double bond was advantageous though a little evidence pointed to that conclusion. The differences observed in normal subjects were small, but, since it seemed possible that subjects having difficulty in fat absorption might show larger differences of some practical significance, we undertook to make such comparisons in a group of poor fat absorbers.

Fat absorption is defective in a number of clinical conditions states in which the external secretion of the pancreas or bile is excluded from the intestine, in celiac disease in tuberculous disease with obstruction of the lacteals, to some extent in marasmic infants and in the new born, in premature infants and twins, in certain infections and post infectious states and particularly in the presence of diarrhea. Some of these conditions are rare and others are difficult to work with since the state of the patient remains constant for a relatively short period of time. The premature group seemed to us the most promising one for comparative studies and we therefore carried out a series of balance experiments in these subjects.

METHODS OF STUDY

The technic of the balance experiments differed somewhat from that employed with mature subjects. Infants of both sexes were used. No attempt was made to put the subjects on a frame, but the feces were collected in diapers of absorbent cotton. The soiled portions of these diapers were carefully removed and placed in an enlarged Soxhlet apparatus where they were extracted for three days first with acidified alcohol and then with ether. This extract was evaporated to

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dryness, the residue taken up in petroleum ether, and the petroleum ether extract filtered, evaporated to dryness and weighed. It was found by blank determinations that a small amount of lipid material could be extracted from the cotton itself, averaging 0.5 gm. for the quantity of cotton employed in typical experiments of five or six days' duration. This value was therefore deducted from the weight of the dried petroleum ether extract to give the actual weight of the fecal lipids for the period.

In the tables which follow, the retention figures are based on the total lipids. However, in view of the possibility that the feces of these infants might contain an unusually large proportion of unsaponifiable material—derived either from intestinal secretions or from contamination with mineral oil which was used in wiping these infants—we also made a series of determinations of the total fatty acids of the feces. It was found in more than a dozen experiments that the percentage retention of the fatty acids differed only very slightly (rarely more than 3 or 4 per cent) from that calculated for the total lipids. We therefore felt that the simpler method of determining the total lipid retention provided a sufficiently accurate measure of fat absorption for our purpose.

The experimental feedings were prepared as in our previous report¹ from skimmed milk with added sugar, in which the various fats were incorporated by homogenization.

RESULTS

In Table I are presented twenty-two experiments on healthy premature infants to whom various fats were given. Our data confirm those of other workers² that these infants absorb fat with difficulty. Only a trifle more than half of the butter fat intake is retained on the average, and in individual periods even less than this. However, when we come to the fats containing predominantly unsaturated fatty acids—olive oil and soy bean oil—we find that retention is much more complete, from 15 to 25 per cent more of the intake is retained. It is apparent that in these infants the difficulty in absorbing fat is such as to be a serious impediment to nutrition when ordinary milk formulas are used, this may in large measure be avoided by the substitution of a more readily absorbable fat.

Similar, though less striking, results were obtained in a pair of full-term twins (Table II). Only the smaller and feebler of these showed differences in fat retention comparable to those observed with premature infants.

It will be noted (Table I) that the retention of soy bean oil is on the average better than that of olive oil, suggesting that the presence of a second double bond is advantageous. Only a few comparisons

were, however made in the same subjects, and it is possible that the infants studied on soy bean oil were better fat absorbers. In Table III we have collected observations made in identical subjects. It appears

TABLE I

FAT RETENTION OF PREMATURE INFANTS ON VARIOUS NATURAL FATS

FAT FED	PERIOD	AGE (MO)	WEIGHT (KG)	DURATION OF EXPERIMENT (DAYS)	FAT INTAKE (GM PER DAY)	FECAL FAT (GM PER DAY)	FAT RETENTION	
							GM PER DAY	% OF INTAKE RETAINED
Butter	C-n, 'A' 2	1½	2.02	5	11.18	4.56	6.60	59.1
	C-n, 'A' 5	2	2.64	5	16.80	5.64	11.16	66.4
	C-n, 'B' 1	1	1.79	5	10.44	4.90	5.54	53.1
	C-n, 'B' 5	2	2.43	5	15.12	4.84	10.28	68.0
	D-t 2	½	1.92	5	11.47	3.70	7.77	67.7
	B-r 1	1½	2.55	5	6.69	2.43	4.22	63.1
	B-r 4	2	3.25	6	21.56	11.38	10.28	47.7
	D-m 3*	1½	3.17	3	17.99	9.29	8.70	48.4
	D-s 1	2	2.56	8	19.99	9.33	10.16	50.8
Average		1½	2.48	5½	14.58	6.28	8.30	56.5
Olive oil	C-n, 'A' 1	1	1.73	5	11.48	4.85	7.13	62.1
	C-n, 'B' 2	1½	2.05	5	10.60	3.45	7.15	67.5
	B-r 3	1½	3.10	6	21.74	4.81	16.92	77.8
	D-m 2	1½	3.05	6	17.58	3.70	13.88	78.9
	K-e 1	1	2.44	5	15.84	4.01	11.88	74.7
	M-s 1	½	2.40	6	14.04	3.71	10.34	73.6
Average		1½	2.46	5½	15.21	4.01	11.21	73.4
Soy bean oil	C-n, 'A' 3	1½	2.16	5	12.94	2.27	10.66	82.5
	C-n, 'A' 4	1½	2.47	5	16.19	2.14	14.06	86.8
	C-n, 'B' 3	1½	2.26	5	12.94	2.60	10.33	79.9
	C-n, 'B' 4	1½	2.49	5	15.93	3.55	12.37	77.7
	W-t 1	½	2.15	6	12.04	1.38	10.67	88.6
	Average	1½	2.31	5½	14.01	2.59	11.62	83.1
Human body fat	B-r 2	1½	2.83	6	19.76	4.90	14.86	75.2
	D-m 1	1	2.75	6	17.66	4.71	12.95	73.3
	Average	1½	2.79	6	18.71	4.80	13.91	74.3

Period terminated because infection developed

TABLE II

FAT RETENTION OF TWO FULL TERM TWINS

PERIOD	FAT FED	AGE (MO)	WEIGHT (KG)	LENGTH OF PERIOD (DAYS)	FAT INTAKE (GM/DAY)	FECAL FAT (GM/DAY)	FAT RETENTION	
							GM/DAY	PER CENT OF FAT INTAKE RETAINED
J S-h 1	Butter	2½	3.45	6	18.27	4.04	14.23	77.9
J S-h 2	Olive oil	3½	3.73	6	18.39	2.75	16.14	85.4
W S-h 1	Butter	2½	3.17	6	16.92	5.72	11.20	66.2
W S-h 2	Olive oil	2½	3.40	4	17.55	1.47	16.08	91.6

These infants were placed on metabolism frames for the collection of excreta as described in our preceding report.

TABLE III
FAT RETENTION OF INDIVIDUAL PREMATURE INFANTS IN CONSECUTIVE PERIODS

SUBJECT C—N "A"			SUBJECT C—N "B"			SUBJECT B—R			SUBJECT D—M		
AGE (MO)	FAT FED	PER CENT FAT RE TENTION	AGE (MO)	FAT FED	PER CENT FAT RE TENTION	AGE (MO)	FAT FED	PER CENT FAT RE TENTION	AGE (MO)	FAT FED	PER CENT FAT RE TENTION
1	Olive oil	62.1	1	Butter	53.1	1½	Butter	63.1	1	Human body fat	73.3
1½	Butter	79.1	1½	Olive oil	67.5	1½	Human body fat	75.2	1½	Olive oil	78.9
1½	Soy bean oil	82.5	1½	Soy bean oil	79.9	1½	Olive oil	77.8	1½	Butter	48.4*
1½	Soy bean oil	90.8	1½	Soy bean oil	77.7	2	Butter	47.7			
2	Butter	66.1	2	Butter	68.0						

*Infection developed at close of period

that on olive oil the percentage retention is sometimes 25 per cent or more better than butter (subject W S—h, Table II, and subjects B—r and D—m, Table III), the difference being comparable to the average figures found with soy bean oil. However, in the two C—n infants, who were studied on both these fats, it is difficult to attribute the somewhat better retention of soy bean oil to age alone.

In order to throw further light on this question of the value of a second double bond, we made some comparisons between pure olein* and linolein.* Studies were made in three infants, the details of which are given in Table IV.

TABLE IV
FAT RETENTION OF PREMATURE INFANTS ON PURE OLEIN AND LINOLEIN

PERIOD	PAT FED	AGE (MO.)	WEIGHT (KG.)	LENGTH OF PERIOD (DAYS)	FAT INTAKE (GM./DAY)	FECAL FAT (GM./DAY)	FAT RETENTION	
							(GM./DAY)	% OF FAT IN STOLEN
K—i 1	Linolein	$\frac{1}{2}$	1.89	5	8.82	2.14	6.68	75.8
K—i 2	Olein	$\frac{1}{2}$	2.03	5	11.97	4.96	7.71	64.4
S—h 1	Linolein	$\frac{2}{3}$	2.02	5	12.47	2.87	9.60	77.0
S—h 2*	Olein	1	2.19	5	13.38	4.17	9.21	68.8
S—h 4*	Linolein	1 $\frac{1}{2}$	2.74	5	12.24	3.64	8.60	70.8
H—m 1†	Olein	$\frac{1}{2}$	2.16	6	9.26	8.88	5.88	68.5
H—m 3†	Linolein	1	2.33	5	18.59	6.77	6.82	50.2
Average—Olein periods		$\frac{1}{2}$	2.13	5 $\frac{1}{2}$	11.54	3.94	7.60	65.6
Average—All linolein periods		1	2.25	5	11.78	3.86	7.93	68.3
Average—Linolein, excluding post infectious periods		$\frac{1}{2}$	1.96	5	10.65	2.51	8.14	76.4

Infection with digestive upset between period 2 and period 4.

†Infection with digestive upset between period 1 and period 2.

In none of these periods was the retention as high as in our previous studies on premature infants. This may have been due to the fact that the feeding contained monoglycerides and diglycerides or to the fact that the infants in this group were distinctly younger. We are inclined to accept the latter explanation, for we observed no untoward effect in normal infants when a similar preparation of olein was fed. In fact our best retention figures were obtained with this material.

The comparisons between the olein and linolein were not as conclusive as we had hoped. Unfortunately an infection developed in the premature ward during the course of this work. We continued our studies on two subjects when the infection and its effect on the digestion were apparently over, but in view of the chemical findings it may

These were prepared synthetically from the pure fatty acids (95 per cent or more pure) and glycerin. The final products contained considerable monoglyceride and diglyceride although the larger part consisted of triglyceride.

be doubted whether either of these infants had completely returned to normal. We are, however, presenting the results *in toto* for what

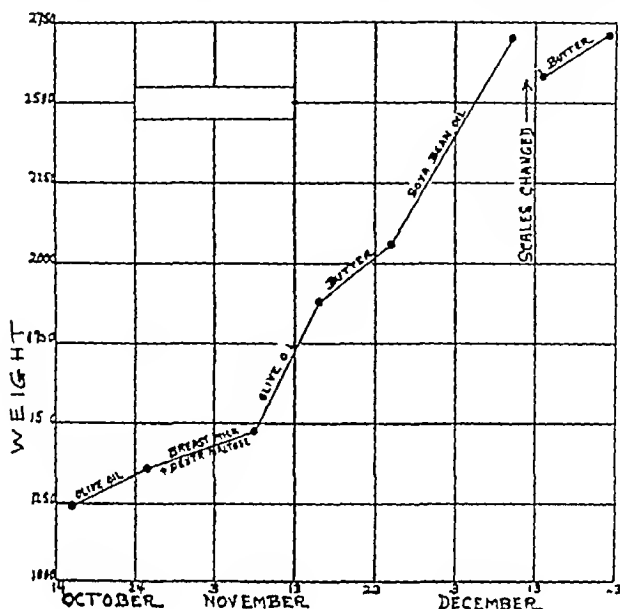


Chart 1—C—n Twin 'A'

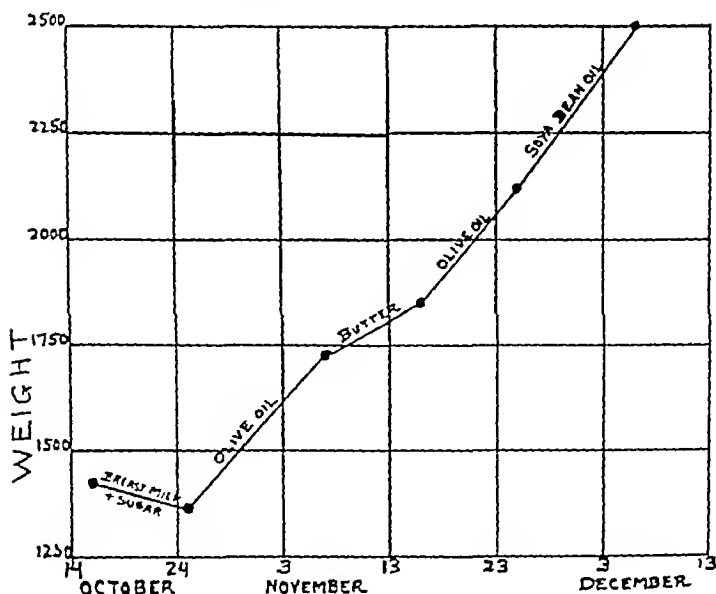


Chart 2—C—n Twin 'B'

they are worth. If we exclude the postinfectious periods, we are left with a pair of unquestionably good periods on infants K—1 and S—h in which the retention of linolein is distinctly better, the effect of age

should have favored the olein, for it was fed when the infants were a week older. Even if we include the postinfectious periods, the linolein still gives a slightly higher average retention figure.

The evidence obtained—either in the comparisons between olive and soy bean oil or in those between olein and linolein—is not conclusive, but it points in the same direction as that obtained by us in our study of normal infants suggesting that an additional double bond possesses a slight advantage from the point of view of fat absorption.

As we have pointed out elsewhere¹ the weight curve may give fallacious information as to the value of a particular type of feeding particularly when it is followed for only a short period of time, the retention of water and electrolytes alone may be responsible for gain

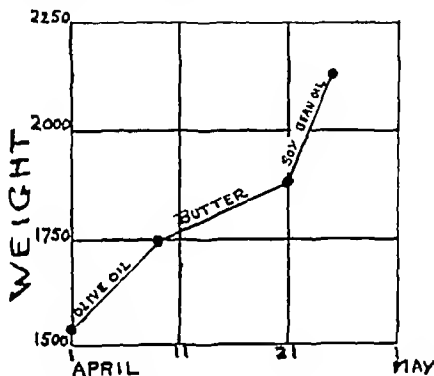


Chart 3—Baby H—J

in weight. Conversely improvement in nutrition may not be immediately shown in the weight curve. However if, as we have reason to believe, the substitution of more readily absorbable fats for butter serves to produce a significant improvement in nutrition, such an improvement might well be reflected in the weight curve. In some of our premature infants little or no change was observed in the weight curve, even though chemical determinations showed that more fat was being absorbed. But in more than half of our cases a striking upturn in the weight curve followed the substitution of olive oil or soy bean oil for butter. Such curves are shown in Charts 1, 2, 3 and 4 and appear to offer confirmatory evidence of the value of the more readily absorbable fats in the nutrition of these patients. Of particular interest are the observations on the identical C—n twins during the first weeks of life. One of these infants was started on a cow's milk

feeding in which olive oil was substituted for butter. This infant gained weight from the start, at no time falling below his birth weight, in contrast to his twin who was fed similar quantities of breast milk with added carbohydrate, in whom the usual postnatal loss of weight occurred.

It seemed of interest to ascertain whether the poor fat absorption of premature infants is associated with difficulty in splitting fat. It will be recalled that the full-term infants studied by us¹ were able to split fat completely, the so-called "neutral fat" fraction of their feces consisting in reality of unsaponifiable material. In order to obtain information upon this point, fat partitions were carried out in fourteen experimental periods on premature infants. In no instance was fat-splitting found to be complete, the true neutral fat of the feces being

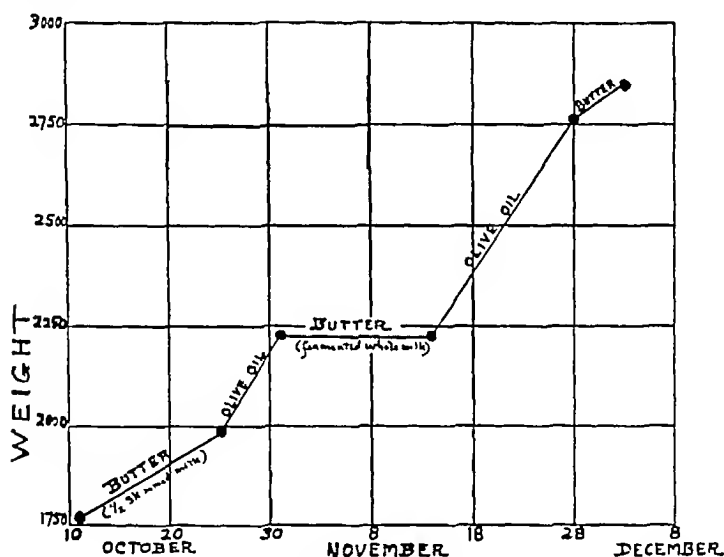


Chart 4 —Baby J—k.

found to exceed 0.2 gm a day on diets of whole milk. The unsaponifiable matter was invariably in excess of that found in full-term infants, indicating that difficulty is experienced in the absorption of this fraction also. We are not prepared to say whether the difficulty in fat absorption in the premature infant is due to poor fat splitting, but at least it is of interest that both functions are impaired in these subjects.

The question may well be raised as to whether the results obtained with premature infants and twins are applicable to other groups of poor fat absorbers. We do not believe that any such generalization is justified, each group will have to be studied independently. A limited experience with infections and postinfectious states has given us the impression that considerably less benefit is to be expected here

from the substitution of olive oil or soy bean oil for butter than with premature infants, the unsaturated acids are by no means spared by the process which interferes with fat absorption. Whether a material gain can be accomplished by changing the fat in these circumstances we are not prepared to say. Ladd³ reported a series of malnourished infants who gained weight more rapidly after the substitution of olive oil for butter fat, his conclusions as to the efficacy of homogenized olive oil were said to be confirmed by metabolism experiments which however, were not published. Other writers⁴ have felt that it was inadvisable to use olive oil in the presence of digestive upsets a judgment which we believe to have been based on the appearance of the stools rather than that of the patient. Naturally, under conditions when much of the food fat appears in the stool, the stools will be more liquid when a liquid rather than a semisolid fat is fed.

CONCLUSIONS

1 We have confirmed observations in the literature that premature infants and twins have marked difficulty in fat absorption.

2 A very striking difference was found in the ease with which they absorb particular fats olive oil and soy bean oil being far more completely absorbed than butter fat.

3 The improvement in nutrition when these fats are substituted for butter is often promptly reflected in the weight curve.

4 Some further evidence was obtained that the presence of more than one double bond in a fatty acid chain favors fat absorption.

5 Fat splitting is less complete in the premature infant than in the full term infant the retention of unsaponifiable material is also impaired.

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STUDIES IN INFANTILE ALLERGIC ECZEMA

II SERUM LIPIDS, WITH SPECIAL REFERENCE TO SATURATION OF THE FATTY ACIDS

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IN CONTINUATION of a study of the serum lipids (cholesterol, phospholipids) in infantile allergic eczema, published in 1933,¹ we had just begun an investigation of the fatty acids when Hansen's² paper on this subject appeared. Wishing to obtain data for comparison with his, we modified our program in some respects and the results here presented cover practically the same ground as those of Hansen. The number of cases, both with and without eczema (normal controls), is, however, considerably larger than in his report.

It will be recalled that Hansen determined cholesterol, total fatty acid, iodine absorption, and the iodine number of the fatty acids in the serum, concluding that the serum cholesterol and fatty acids in eczema are slightly less than in normal controls and that the serum fatty acids are less unsaturated; hence, that the unsaturated fatty acids should be given consideration as an etiologic factor in the disease.

Methods—Cholesterol was determined by the method of Myers and Wardell³ on the dry residue left by evaporation of the alcohol ether extract but without preliminary saponification, as Bloor⁴ recommends. Hansen used Bloor's method. It is generally believed that the two show good agreement.

For fatty acids, the method of Bloor⁴ was followed except that the alcohol ether extract was kept at the boiling point for one minute instead of the "few seconds" recommended by Bloor, which appeared to be insufficient. Hansen also used Bloor's method.

Iodine numbers were determined by Yasuda's⁵ method, based upon that of Rosenmund and Kuhnemann but without preliminary saponification, an omission recommended by Page, Pasternak, and Burt⁶ whose modification was followed by Hansen. It would appear that the results of the method used by Hansen and by ourselves are fairly comparable.

In one important respect our procedure differed from that of Hansen. Because of the fact that our patients were seen in the out patient department we were unable, as Hansen was able, to obtain fasting samples. Most of our patients had been fed one to four hours before collection of the blood. Theoretically this constitutes a

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serious objection to our figures. Comparison, however, with those of Hansen shows that in the normal group our figures for total fatty acids are considerably lower on the average than those of Hansen and in the eczema group only slightly higher also the iodine numbers in the normal groups in the two series show no significant differences. We are therefore inclined to believe that the time of bleeding in the two series plays a relatively small part in such quantitative differences as were observed. We have included a few older children in our series, but nearly all were within the same age limits as those of Hansen's series that is, from five to eighteen months, and those outside these limits did not materially alter the averages.

In our series were sixteen normal individuals and fifteen with allergic eczema

TABLE I
No ECZEMA (16 CASES)—NORMAL CONTROLS

CHOLESTEROL	TOTAL FATTY ACIDS	TOTAL LIPIDS	IODINE NUMBER	AGE
172	338	510	124	6 mo
211	324	535	124	11 mo.
169	181	350	117	3½ mo
141	195	336	114	7 mo
213	340	553	107	5 mo
162	229	391	125	5 mo
124	307	430	86	2 mo
121	299	420	111	10½ mo
346	328	674	130	7 yr
129	331	460	100	5 mo
199	322	521	117	3 yr
143	252	395	117	3 yr
122	297	418	108	18 mo.
169	371	530	121	23 mo
142	291	433	152	7 mo.
207	274	431	131	10 mo
Av 161	290	451	117	

TABLE II
ECZEMA (15 CASES)

CHOLESTEROL	TOTAL FATTY ACIDS	TOTAL LIPIDS	IODINE NUMBER	AGE
222	391	613	105	5 mo
141	379	520	102	3 mo
134	315	449	120	5 mo
136	383	468	97	6 mo.
163	381	544	107	8 yr
162	473	634	111	11 mo
198	339	537	101	15 mo
136	265	401	104	24 mo
142	289	430	112	11 mo
220	436	657	87	7 mo
169	295	464	135	3½ mo.
163	254	492	140	10½ mo.
213	405	618	102	18 mo
173	358	532	102	4½ mo
138	318	456	80	2½ mo.
Av 168	351	516	107	

TABLE III
SUMMARY AND COMPARISON WITH HANSEN'S DATA

	NO CASES		CHOLESTEROL		TOTAL FATTY ACIDS		TOTAL LIPIDS		IODINE NUMBER	
	OUR CASES	HANSEN'S CASES	OUR CASES	HANSEN'S CASES	OUR CASES	HANSEN'S CASES	OUR CASES	HANSEN'S CASES	OUR CASES	HANSEN'S CASES
Averages										
Normal	16	6	161	185	290	361	451	546	117	111
Eczema	15	7	168	147	351	342	516	488	107	84
Range										
Normal			121	142	181	292	336	434	86	100
			346	232	340	411	674	643	152	136
Eczema			184	118	254	261	401	409	80	69
			222	160	473	443	657	586	140	104

COMMENT

Cholesterol—In a previous study¹ of a different series of infants with eczema we found a considerable proportion with hypercholesteremia. It is instructive to find that in the present subsequent series the cholesterol was uniformly within normal limits and the average was almost exactly that of the normal controls. Hansen's figures, by contrast, show a much lower figure for the normals and a higher one for the eczema cases than our own.

Total Fatty Acids—Our average figures for the patients with eczema are not notably different from those of Hansen (351 and 342, respectively) but in the normals are considerably lower (290 as compared with 361), and this is also true of the total lipids. The contrast between the normal and the eczema group in our data is the reverse of that in Hansen's, ours showing a higher figure in the eczema group, and Hansen's a slightly lower one.

Total Lipids—The same difference as in total fatty acids, between our figures and those of Hansen, is seen in total lipids (sum of cholesterol and fatty acid) but to a somewhat more marked degree, our eczema group being about 14 per cent higher than the controls, and Hansen's about 10 per cent lower.

Iodine Numbers—For the control group our average (117) is not significantly different from Hansen's (111). In our eczema group the average (107) is about 9 per cent below that of the normals, while in Hansen's it (84) was about 24 per cent below his normal average. An arrangement of the individual data in our series in order of magnitude brings out a fairly striking tendency to lower figures in the eczema group, which is somewhat obscured in the average by the effect of two high figures. Our data, therefore, support Hansen's conclusion that in eczema the fatty acids of the serum show decreased unsaturation as compared with those in normal children, but, in a quantitative sense, the degree of saturation is much less, both absolutely and also relatively to the controls.

It may be added that Dr Donald C Marshall, in a considerable number of cases of active eczema admitted to the Children's Clinic of this institution, has been unable to detect any clinical benefit from the administration of unsaturated fat in the form of corn oil, an observation not in accord with Hansen's later report⁷

CONCLUSIONS

1 An investigation of the serum lipids in thirty-one infants and young children, fifteen with infantile allergic eczema and sixteen without that disorder (normal controls) showed that the individuals with eczema had (a) a very slightly higher average cholesterol, (b) considerably higher average total fatty acids and (c) total lipids, and (d) a moderately lower average iodine number for the fatty acids.

2 Our results confirm those of Hansen in that the serum fatty acids of patients with eczema tend to be less unsaturated than those of normal individuals. The degree of unsaturation in our patients with eczema did not, however, depart so far from the normal as was the case in Hansen's series. Our own experimental data and clinical experience have not convinced us that the factor of fatty acid saturation is of primary etiologic significance in eczema. We are rather inclined to regard it as secondary or incidental.

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THE EFFECT OF FEVER THERAPY ON RHEUMATIC CARDITIS ASSOCIATED WITH CHOREA

WITH A PRELIMINARY REPORT ON FEVER THERAPY IN RHEUMATIC CARDITIS WITHOUT CHOREA

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I FEVER THERAPY IN CHOREA WITH CARDITIS

OVER two hundred attacks of chorea have been treated on the Children's Medical Service of Bellevue Hospital with fever induced by the intravenous injection of triple typhoid vaccine. In this series there were sixteen children with definite signs of active carditis at the time of treatment and in addition twenty-seven others with clinically inactive rheumatic heart disease. Of the twenty-seven with inactive heart disease, seventeen had mitral insufficiency, nine had mitral insufficiency and stenosis, and one had mitral insufficiency and stenosis and aortic insufficiency and stenosis.

Because it has been frequently suggested that the presence of advanced heart disease or the presence of active carditis is a contraindication to this form of therapy, the group with active carditis is now being reported in detail.

Our criteria for the diagnosis of active carditis were

- 1 Fever
- 2 Tachycardia
- 3 Change in the quality of the heart sounds
- 4 Presystolic gallop sound
- 5 Development of new murmurs
- 6 Change in the quality of the murmurs present, especially the presence of a high-pitched, shrill, musical quality in the apical systolic murmur (sometimes described as "sea gull" quality)
- 7 Change in rhythm (heart-block, or loss of sinus arrhythmia)
- 8 Electrocardiographic changes, chiefly prolongation of the P-R and QRS intervals
- 9 The presence of subcutaneous rheumatic nodules

While every case did not present all of the above findings, each one presented two or more and the diagnosis of activity was made by at least two observers. In a few cases the diagnosis was made only on going back over the records. In these cases frequent notes on the

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heart were not always made, so that it has been sometimes difficult to determine exactly when the signs of carditis subsided. In the majority of cases, however, the diagnosis was made before the beginning of fever therapy, the patients were watched with especial care and frequent notes on the heart signs were made.

Besides the cases which are being presented, there was one child who had signs of activity on admission to the hospital, but these had disappeared before the beginning of treatment, and seven children in whom the presence of activity was suspected but in whom it could not be diagnosed on any objective basis. We appreciate the fact that there are cases in which the signs of cardiac activity subside promptly after a short time at rest in bed, but on the other hand the tendency to chronicity of the rheumatic infection is well known. We have observed many individuals in whom signs of subacute carditis *i. e.*, tachycardia, gallop, low grade fever, weight loss, etc. persist for months in a child in the hospital. We also realize that there must have been other children in this series with a subacute carditis who gave no clinical signs. In this group would fall those children who presented no signs of heart disease during their attacks of chorea but who after varying intervals without further rheumatic attacks have appeared in clinic with definite organic heart disease. This group will be presented in a later paper. The only case which came to autopsy demonstrates this point well; this was reported in detail in a previous paper.¹ During her two admissions to the hospital the child had never shown any signs of cardiac involvement. There was an inconstant short systolic murmur along the left sternal border but there had never been an apical murmur, and there was no cardiac enlargement. At autopsy, besides a hemorrhagic lobular pneumonia there was an acute verrucose mitral valvulitis and chronic rheumatic valvulitis at the base of the aortic valve.

While we have not yet demonstrated that the disappearance of the signs of activity was the direct result of the fever therapy we feel that their disappearance in the majority of cases by the time of the end of treatment is striking. Certainly the children were not harmed by this form of therapy.

Cases reports of the sixteen patients who had chorea and also carditis follow.

CASE 1—Y. A., eight years old, was admitted Oct. 21, 1932 and discharged Mar. 31, 1933. This child had been followed closely for two years as a tuberculosis contact case. She had had growing pains for six months previous to admission but no other rheumatic history. Two weeks before admission no cardiac murmurs were heard. She was admitted after one week of mild choreiform movements. At that time tachycardia and an apical systolic murmur were present; two days later a middiastolic murmur at the apex was heard; the following day she had an acute arthritis of one finger. Her temperature was normal. White blood cells numbered 8750 with 77 per cent polymorphonuclear leucocytes. Electrocardiograms showed no

significant changes. Treatment for the chorea was begun on the fifth day after admission, fever was induced six times in eight days. The day following the end of treatment, the systolic murmur was softer and the diastolic barely perceptible. Ten days later the heart was slow and regular, rate, 78 with sinus arrhythmia. The day after the completion of treatment an urticarial rash developed, thus lasted for two or three days only. Six weeks later typical erythema marginatum, which persisted off and on throughout the rest of her stay, appeared, but no further signs of active carditis developed. On discharge five months after admission the heart was not enlarged clinically or by x ray, but systolic and presystolic murmurs were present at the apex. She was not seen from the time of discharge until the following autumn, owing to lack of cooperation of the parents, but on return to clinic in December, 1933, seven months after discharge, she had gained 14 pounds and showed no evidence of rheumatic activity. Since then she has been followed regularly both in the tuberculosis clinic and in the chorea clinic, without further evidence of rheumatic infection until June, 1934, when she was readmitted to the hospital with indefinite signs of carditis.

CASE 2—M. B., six years old, was admitted June 20, 1933, and was discharged July 7, 1933. She had no rheumatic history until three weeks before admission when she complained of pain in the ankles, tired easily, had a series of severe epistaxes, and bruised more easily than usual. One week before admission choreiform movements developed. On admission she had a temperature of 100.4° F., mild choreiform movements, many small purpuric spots on trunk and extremities, an enlarged heart with tachycardia, marked presystolic gallop, an apical systolic murmur transmitted to the axilla and base, and a loud, rough, low pitched middiastolic murmur. Electrocardiogram showed right deviation of the electrical axis. White blood cells numbered 8,400 with 76 per cent polymorphonuclear leucocytes. Treatment for the chorea was begun on the fourth day after admission, fever therapy was given six times in eight days. The heart rate had slowed down somewhat before the beginning of treatment, but the gallop and diastolic murmur were still present. The day after the end of treatment the gallop had disappeared, rate was 80 per minute, sinus arrhythmia was present, murmurs were the same. Three days later the diastolic murmur had disappeared, but a third heart sound was heard. Ten days after the end of treatment the rate was 70, sinus arrhythmia was present, sounds were of good quality, there was a soft systolic murmur at the apex, slightly transmitted to the axilla, but no diastolic or third heart sound. One month later she had a tonsillectomy under ether anesthesia with no exacerbation of signs of carditis, and she was discharged to the country in good condition with a cardiac diagnosis of enlarged heart, mitral insufficiency, Class I. She remained in the convalescent home for three months and, having gained 6 pounds, returned to the clinic. Her general condition was good in the winter of 1933-34, and her weight gain satisfactory in spite of the bad home conditions under which she lives. Her present cardiac diagnosis is enlarged heart mitral insufficiency, and (?) stenosis, Class I.

CASE 3—M. A. B., aged seven years, was admitted May 1, 1933, and was discharged July 28, 1933. She had no previous history of rheumatic fever. She was admitted with a history of severe chorea of three months' duration and had been in bed, unable to walk for five weeks. On admission the child was emaciated, dehydrated, and totally incapacitated by an extremely severe pseudoparetic type of chorea. A nodule was present above the left patella. The heart rate was 130/140, there was a marked presystolic gallop, a widely transmitted apical systolic murmur with a high pitched, shrill, musical quality, and a short presystolic murmur. There was no fever, white blood cells numbered 12,400 with 74 per cent polymorphonuclear leucocytes, the electrocardiogram showed no significant changes. Fever treat

ment for her chorea was begun on the fourth day. She was given fever fourteen times in two courses, covering a total period of twenty six days. By the fourth day after the beginning of treatment, the heart rate had come down to 104 and sinus arrhythmia had reappeared but the gallop and high pitched shrill quality of the systolic murmur persisted. Three days later this murmur was much lower pitched and softer and by the tenth day after the beginning of treatment the gallop had disappeared, the rate was 80, the shrill quality of the apical systolic murmur had entirely disappeared and the nodule had also disappeared. One month later the gallop reappeared for ten days with a peridental abscess and fever. Later tonsillectomy was performed without exacerbation of her cardiac signs. On discharge the x ray pictures showed no cardiac enlargement there was a soft systolic murmur at the apex slightly transmitted toward the axilla and an inconstant third heart sound. She was discharged to a convalescent home where she remained for about two months. She was well on return having gained 7 pounds, but shortly after her return she again developed chorea, this time with no evidence of carditis. She was readmitted and remained in the hospital for three months and was then sent to a convalescent home for two months more. On her first return visit to clinic, Apr 11 1934, her temperature was 100.6 F and she had a gallop and tachycardia. She was sent home to bed and about ten days later when choreiform movements began, she was admitted to the hospital. Fever therapy was again given with subsidence of the chorea and disappearance of the signs of possible carditis.

CASE 4—A C. nine years old, was admitted May 2 1933, and was discharged June 3 1933. She had a history of polyarthritis at five and one-half years and of three previous attacks of chorea. Two and a half months before admission, in the clinic, tachycardia and a gallop were noted. she was sent home to bed with a request to return to clinic in two weeks, but she did not. Three weeks before admission she began to have joint pains, and one week later chorea developed. On admission it was found that she had lost 6 pounds since her previous visit to the clinic. she showed moderate choreiform movements an enlarged heart with double mitral murmurs tachycardia and a gallop. The temperature was 100.6 F white blood cells numbered 10,000 with 90 per cent polymorphonuclear leucocytes. the electrocardiogram showed no significant changes. Treatment was begun on the second day after admission. fever was induced eleven times in sixteen days. The gallop began to grow less marked eight days after the beginning of treatment and had entirely disappeared by the last day of treatment. She was discharged to convalescent home one month after admission with a cardiac diagnosis of enlarged heart mitral insufficiency and stenosis. Class IIa. Since that time she remained well, gaining 20 pounds in the past year, until a few weeks ago when she was readmitted to the hospital with signs of active carditis but without chorea.

CASE 5—A C., aged ten years, was admitted May 4 1933 and was discharged July 28 1933. She had had two previous attacks of polyarthritis. Two weeks before admission she had had pain in her legs acute arthritis of the left knee, and fever of 103 F. one week later chorea began. On admission she showed mild choreiform movements erythema marginatum on arms and trunk and enlarged heart with poor quality sounds a rough systolic murmur at the apex, transmitted to the axilla, a rate of 130/140 with a marked gallop. A soft diastolic murmur was first heard two days after admission. Temperature was 101 F on admission and remained elevated at 100 to 100° F during the eight days preceding treatment. White blood cells numbered 8500 with 70 per cent polymorphonuclear leucocytes; the electrocardiogram showed no significant changes. Acute arthritis of the right knee developed on the first day after admission. Beginning on the ninth day after admission she was given fever six times in six days. The heart rate became some-

what slower, and the quality of the heart sounds improved although the gallop persisted and was still heard three weeks after the end of treatment. There then followed sixteen days before another note on the heart was made, which said "No gallop, rate is slow, sinus arrhythmia, systolic and diastolic murmurs are definite, the diastolic follows a fairly loud second sound, this is often confused with a true gallop." It is therefore possible that the gallop had disappeared earlier than a review of the chart would indicate. She was discharged to a convalescent home where she remained for one month. During the winter of 1933-34 she was well, with steady weight gain, but in July, 1934, she again showed signs of active infection, with joint pains, epistaxes, slight weight loss, and occasional low grade fever.

CASE 6—A B C, eleven years old, was admitted Apr. 27, 1933, discharged June 10, 1933, readmitted Aug. 9, 1933, and discharged Sept. 6, 1933. Three years previously she had had chorea and carditis following appendectomy. The April admission was for four days of chills, fever, pain in the chest, and "bloody urine." On admission temperature was 101° F, she appeared acutely ill, had an acute pharyngitis, an enlarged heart with double mitral murmurs, a much accentuated P₂, and tachycardia. The first urine examination showed 75 mg of albumin, rare hyaline casts, from 2 to 3 red blood cells and from 8 to 10 white blood cells per high power field. Subsequent examinations continued to show a faint trace of albumin although the microscopic examination rapidly became negative. She ran an irregular fever to 101° F for a week following admission, her temperature was then normal for three days. At this time choreiform movements began to be noticed, and she again began to run fever of 100° to 102° F. Five days after the beginning of the chorea a gallop was heard, and the P₂ became even more accentuated. The chorea had progressed rapidly in severity until it was classed as "severe moderate." Electrocardiogram on May 2, 1933, five days after admission, showed a rate of 88, P R interval of 0.2 seconds, QRS interval of 0.08 seconds with a prolonged S T interval in Lead I. Ten days later the day of the beginning of treatment, the P R interval was still 0.2 seconds, QRS interval was 0.06 seconds, low and slurred, and there was slight right deviation of the electrical axis. Fever treatment for chorea was begun on the seventh day after the first abnormal movements were noted, and four febrile reactions in six days were sufficient to cause almost complete subsidence of her chorea. By the third day after the beginning of the treatment the gallop had disappeared, the P₂ had become less loud, and the rate was 100, the following day an electrocardiogram showed no significant changes, the rate being 92 and the P R interval 0.16 seconds. She was discharged to a seaside convalescent home, perhaps somewhat sooner than she should have been, and was sent home after only a short stay there. She was apparently comparatively well at home for five or six weeks when chorea began again, and after one week she was readmitted. On admission choreiform movements were very mild, she had tachycardia and a gallop with a very loud snapping P₂. Temperature was normal, as were the white blood count and differential blood count. Because of the mildness of her chorea, she was observed for fifteen days before being given fever treatment, during which time the tachycardia and gallop disappeared, and the quality of the heart sounds improved. She was then given fever six times in eight days, during which time there was no reappearance of clinical signs of carditis. Two weeks following the end of treatment, an aortic diastolic murmur was first heard, which persisted. Three weeks later, having gained 5 pounds since admission, she was discharged to convalescent home, with a cardiac diagnosis of enlarged heart, mitral insufficiency and stenosis, aortic insufficiency, Class IIa. She remained in the convalescent home for three months and returned in January, 1934, having gained thirteen pounds during her stay. She continued to gain weight and do fairly well throughout the winter on a regime of extra rest and limited activity, until about the first of May, when

she began losing weight, having some fever, dyspnea, and precordial pain she was readmitted to the hospital. She went steadily downhill developing acute pericarditis with effusion, congestive failure, and acute glomerular nephritis she died three and one-half weeks after admission. Autopsy showed active and inactive mitral and aortic valvulitis, active tricuspid valvulitis acute fibrinous pericarditis chronic adhesive pericarditis, and acute diffuse glomerular nephritis.

CASE 7—A. D., aged six years was admitted June 29, 1932 and was discharged Aug 1, 1932. She had no previous rheumatic history Six weeks before admission choreiform twitching had followed chickenpox and became progressively worse, especially since measles four weeks before admission. For one week she had had joint pains. On the day of admission, examination of the heart was negative the chorea was severe with generalized hypotonia. The following day she developed acute arthritis of the right ankle and right great toe a blowing systolic murmur at the apex transmitted to the anterior axillary line and to the base was heard there was a gallop and tachycardia and an accentuated P₂. Temperature was 101 F, and white blood cell count was 9050 with 89 per cent polymorphonuclear leucocytes. The electrocardiogram taken one week later showed no significant changes. Temperature remained elevated for three days and was then normal for four days before the beginning of treatment. During this time the cardiac signs improved somewhat the rate became slower but the gallop persisted. Fever was then induced seven times in seven days. Two days after the end of treatment there were no clinical signs of active carditis rate was slow and regular there was no gallop there was a systolic murmur at the apex transmitted toward the axilla, and the P was somewhat accentuated. The x ray examination, however showed no definite cardiac enlargement. She was discharged to the country in good condition one month after admission. She remained in convalescent home for two and one-half months and has been followed regularly in clinic for the two years since that time. Weight gain has been satisfactory, and there has been no evidence of active infection at any time. At present her heart is not enlarged, and no murmurs can be heard.

CASE 8—H. D. ten years old was admitted Feb 8 1932, and was discharged Oct. 22 1932. She had had polyarthritis at the age of three years, heart disease had been discovered when she was five, and she had had a second attack of polyarthritis followed by acute pericarditis with effusion at the age of seven. She had been followed in the cardiac clinic without recurrence since that time. She was admitted with a history of pain in the right knee and ankle and fever for two weeks. On admission her temperature was 101 F she was pale and listless but not acutely ill her right ankle was tender and painful but not acutely inflamed there was tachycardia and an apical systolic murmur transmitted to the axilla. Four days after admission an apical diastolic murmur which persisted was heard. White blood cells numbered 12,100 with 80 per cent polymorphonuclear leucocytes. Although the signs were not definite, she was thought to have active carditis. For the next seventeen weeks there was little change in her condition. Her joint symptoms subsided, and she gained weight, but her temperature remained elevated for the most part between 100 and 101 F with occasional rises to 102 associated with an acute pharyngitis. Her heart signs remained the same, and, although they were not clear cut, she was thought to have continued rheumatic activity in her heart. She was given two blood transfusions for a marked anemina, but she remained pale and listless. During the eighteenth week of her stay in the hospital she had a sore throat and temperature of 101.3 F four days later she complained of pain in her shoulder, and the next day choreiform movements were first noticed. At this time there was tachycardia, and a gallop was noted. She was observed for five days, during which time the chorea became more marked her temperature remained elevated from 100 to 101 F, and the tachycardia and gallop persisted.

Fever was then induced six times in seven days. The day following the second fever, the gallop was no longer heard, and the heart rate was 100. Following the end of treatment the rate was 80, rhythm was regular, and there was no gallop or other clinical signs of active carditis. Her temperature, which remained below 100° for eleven days following treatment, again became elevated for about ten days during another attack of acute pharyngitis. Four days after the subsidence of this attack and about one month after the end of fever treatment, the electrocardiogram showed first stage heart block. The only previous electrocardiogram which had been taken was one week earlier, this showed a P R interval of 0.19 seconds. Electrocardiograms taken every three days continued to show a block for eight days although during this time there were no clinical signs of activity. For the next two months her temperature remained normal, she continued to gain weight, and her general condition was fairly good. She then had a secondary tonsillectomy followed by an elevated temperature for about a week. When this subsided, she was discharged and sent home. Since her discharge almost two years ago, she has been followed in the clinic and has been doing, on the whole, fairly well. In the spring of 1933 she had a mild flare up with arthritis and fever without signs of active carditis, this attack subsided on rest in bed at home. She returned to school in the fall of 1933 and continued throughout the winter 1933-34 without evidence of active infection, but in July, 1934, again developed polyarthritis and was admitted to another hospital.

CASE 9—C G, nine years old, was admitted Jan. 19, 1934, and was discharged Feb. 27, 1934. She had no previous rheumatic history. Choreiform movements began two weeks before admission, following a two week illness of fever and rash. On admission she had severe chorea with marked hypotonia, heart was not enlarged, and no murmurs were heard, the rate was 144, and a marked presystolic gallop was present. The following day a systolic murmur at the apex and left sternal border was heard. Treatment was begun on the fourth day after admission, fever was induced seven times in eight days. The day following the first treatment, the gallop was no longer heard, and the heart rate had fallen to 100/112. By the fifth day of treatment the rate was 88, sounds were of good quality, and the systolic murmur had become less loud. Ten days following the end of treatment, the murmur was no longer heard. She was discharged to convalescent home in good condition with no abnormal findings in the heart, although the x-ray examination showed questionable slight enlargement. She remained in the country for six weeks where her weight gain was good. In June of this year she again developed chorea, but without any signs of carditis, and was admitted to the hospital and treated. No murmurs were heard at any time during this admission, and the heart showed no enlargement.

CASE 10—M H, aged eight years, was admitted Dec. 28, 1932, and was discharged Mar. 29, 1933. Though she was the youngest child in a rheumatic family, she herself had no known previous history of rheumatic fever, however, a systolic murmur at the apex had been heard following scarlet fever seven months before admission. Choreiform movements began from three to four weeks before admission, and fever had been present for three or four days. On admission she showed mild chorea, her heart was not enlarged, there was a tachycardia of 130, a much accentuated P₂, and at the apex a low pitched, rather rough and loud systolic murmur transmitted only slightly. Temperature was 101° F and continued to be elevated for three days, white blood cells numbered 10,400 with 86 per cent polymorphonuclear leucocytes. The electrocardiogram showed no significant changes. Three days after admission a mitral diastolic murmur was heard. The diagnosis of activity was somewhat questioned, but the presence of fever and tachycardia, the quality of the heart sounds, and the development and subsequent disappearance of a diastolic

murmur made it seem likely. Treatment was begun on the ninth day after admission, fever being induced four times in five days. At the time of the beginning of treatment the tachycardia had subsided, but the diastolic murmur was still present. On the last day of treatment the diastolic murmur was no longer heard. She was given prolonged rest in bed following the treatment she gained five pounds and except for an infected finger, made an uneventful recovery. On discharge there was a short untransmitted apical systolic murmur and the x ray examination showed no enlargement. She was sent to a convalescent home where she remained four months. She was not brought back to the clinic until November 1933, five months after her return from the country when both she and her sister had had mild "twitchings" for several weeks. Although her chorea was very mild and there was no evidence of active carditis she was admitted to the hospital because of the impossibility of adequate care at home. Her chorea subsided without treatment, and she was sent home in five weeks. Since that time she has done only fairly well. Weight gain has been irregular, she has had two attacks of cervical adenitis and sore throat on her last visit to clinic in June 1934, she had one small area of erythema on her arm and activity of her rheumatic infection was suspected. We have been unable to persuade her mother to bring her into the clinic since that time. Her cardiac diagnosis when last seen was enlarged heart mitral insufficiency Class I.

CASE 11—T J., two years and ten months old, was admitted June 18 1933, and was discharged June 29, 1933 he was readmitted July 7 1933, and discharged Aug 1 1933. He had no previous rheumatic history. Choreiform movements had been present for one week. On admission he showed moderate chorea, an enlarged heart with a high pitched, shrill, musical systolic murmur tachycardia of 130/140 and a presystolic gallop. An apical diastolic murmur was definitely heard the day following admission. Temperature was normal white blood cell count was 12,500 with 78 per cent polymorphonuclear leucocytes. Treatment was begun on the ninth day after admission. Fever had been given six times in eight days when he developed chickenpox and had to be transferred to a contagious disease hospital. On discharge his heart rate was 104 the apical systolic murmur was still high pitched and shrill, but the gallop had become protodiastolic in time. He was readmitted from the contagious disease hospital eight days later, when he showed no evidence of active carditis. His heart was unquestionably enlarged clinically and definitely so by x ray examination the rate was slow and there was sinus arrhythmia there was a soft systolic murmur at the apex transmitted a short distance toward the axilla and along the left border of the sternum to the base, and a short diastolic murmur at the apex. On discharge three weeks after readmission the diastolic murmur was no longer heard. During the winter of 1933-34 he has improved remarkably having shown no evidence of recurrence of the rheumatic fever. At present his heart is not enlarged and no murmurs can be heard.

CASE 12—L B., aged eleven years, was admitted May 28, 1933, and was discharged June 18 1933. He had no previous rheumatic history. Three weeks before admission he had his first attack of hives, which had persisted to the time of admission. One week before admission choreiform movements had begun and had progressed rapidly so that on admission he presented a severe pseudoparetic chorea. His heart showed no enlargement clinically the rate was 120 there was no sinus arrhythmia there was an accentuated P_2 and a loud apical systolic murmur with a high pitched, shrill musical quality transmitted to the axilla. Temperature was 102° F and remitted elevated for two days before treatment. White blood cells numbered 12,850 with 81 per cent polymorphonuclear leucocytes. Fever was induced nine times in eleven days. During the period of treatment the shrill quality of the systolic murmur became less marked although it did not entirely dis-

appear until one week after the end of treatment, when the rate was 100 and sinus arrhythmia had returned. Nine days following treatment, the parents insisted on taking the boy home against advice, and it has been impossible to persuade him to return to clinic since that time.

CASE 13—I. K., six years old, was admitted June 28, 1933, and was discharged Aug 6, 1933. She had had no history of rheumatic fever until one month before admission when she had polyarthrits, followed in three weeks by choreiform movements. On admission her temperature was 103.6° F, there was an acute arthritis of the left wrist, severe choreiform movements with hypotonia, a questionable nodule on the scalp (which subsequently disappeared), her heart was not enlarged, the rate was 144/160, there was a slightly transmitted soft blowing systolic murmur and a questionable gallop. White blood cell count was 13,700 with 60 per cent polymorphonuclear leucocytes. Electrocardiogram showed only sinus tachycardia. Her temperature fell gradually to normal in six days, heart rate became slower, although still definitely accelerated, and the systolic murmur became much louder. Treatment was begun on the ninth day after admission. Fever was given six times in nine days with rapid marked improvement in her chorea. During the treatment a short diastolic murmur was heard for several days. By the end of treatment the heart rate was 112, sinus arrhythmia had reappeared, and the questionable gallop and the questionable nodule had disappeared. One week later the heart rate was 84 and remained down for the rest of her stay. On discharge the x ray examination showed no cardiac enlargement, and there was only a soft untransmitted apical systolic murmur. She did beautifully for six months after discharge, gained weight well, and was entirely free from signs of rheumatic activity. She was therefore allowed to return to school in February, 1934. Four days later she developed severe polyarthrits and was readmitted to the hospital. On admission besides polyarthrits, she had a very severe carditis and later developed chorea. She remained in the hospital three and one-half months and was recently sent home to remain in bed, very much improved, although with signs of low grade activity still present.

CASE 14—A. L., nine years old, was admitted Dec 14, 1932, and was discharged May 3, 1933. She had had severe chorea without signs of carditis six months before, but no other rheumatic history. Her present attack began two weeks before admission. On admission she had moderate choreiform movements and a temperature of 102.6° F, which remained elevated for the week preceding treatment. Active carditis was suspected because of tachycardia, an extremely labile pulse rate, and the recent appearance of a short diastolic murmur. Six days after admission the heart rate was 120, a definite gallop was heard, the electrocardiogram showed a P R interval of 0.21 seconds, and the chorea had become severe. Treatment was begun on the ninth day, fever being induced twelve times in seventeen days. The fifth day after the beginning of treatment, the pulse was 80/90, and the gallop was no longer heard. From then on throughout the remainder of the treatment and of her stay in the hospital, the pulse rate remained down and no further evidence of carditis appeared. An electrocardiogram made after the second treatment showed a P R interval of 0.18 seconds, and one taken one week later, a P R interval of 0.14 seconds and sinus arrhythmia. On discharge following tonsillectomy three months later, the x ray examination showed no cardiac enlargement, there was a soft, blowing, systolic murmur, maximum at the apex, and transmitted just to the left of the apex and to the base, and a short middiastolic murmur. Six weeks after discharge no diastolic murmur was heard. At this time, about five months after the clearing of her previous attack, she again developed chorea, this time of moderate severity, but without any evidence of active carditis. She was readmitted and given fever therapy.

Since her discharge in August, 1933, she has done well without any recurrence of chorea or carditis. Her cardiac diagnosis is enlarged heart, mitral insufficiency Class I

CASE 15—M R. ten years old was admitted Nov 14, 1930 and was discharged Dec. 23, 1930. She had had one previous attack of chorea at the age of six years but no other rheumatic history. The present attack, following a head cold began two days before admission. On admission she showed mild chorea, a heart slightly enlarged to the left, tachycardia and gallop, poor quality heart sounds, and a soft systolic murmur at the apex, transmitted to the axilla. By the first day of the treatment, the sixth day after admission, the rate was somewhat slower but the gallop was still definitely present. Fever treatment was given seven times in seven days. The day following the last treatment, the heart rate was 88 rhythm was regular, no gallop was heard and the systolic murmur had become fainter. For the remainder of her stay the rate remained down, and no further gallop was heard. A late soft diastolic murmur was heard at the apex from about one week after the end of treatment for ten days, but it was not heard during the last two weeks of her stay. The x ray pictures showed cardiac enlargement with accentuation of the right auricular and left ventricular curves. She was discharged with a diagnosis of enlarged heart and mitral insufficiency. Since that time she has had two mild attacks of chorea, one in July, 1931, which was treated with fever therapy and one in April, 1932, which subsided on rest in bed alone. For the past two years she has had no chorea or other evidence of rheumatic activity, her heart no longer shows enlargement either clinically or in x ray pictures, and there is only a very faint systolic murmur best heard along the left sternal border. In October, 1933 she began to lose weight rapidly and to run an irregular afternoon fever. She was admitted to the hospital and when found to have tuberculosis (childhood type of primary lesion) she was transferred to a tuberculosis hospital.

CASE 16—S T, aged five years, was admitted Apr 25 1932, and was discharged June 3 1932. He had no previous history of rheumatic infection. Choreiform movements had begun three weeks before admission and one week after the onset he had pain for one day in his right knee and ankle. On admission he had moderate chorea with moderate hypotonia, a clinically enlarged heart, with a much accentuated P₂, a gallop no tachycardia (pulse 80/90) a loud blowing apical systolic murmur with a high pitched, shrill, musical quality, transmitted to the axilla and base, and a short, rough middiastolic murmur. His temperature was normal white blood cells numbered 6,100 with 75 per cent polymorphonuclear leucocytes the electrocardiogram showed right deviation of the electrical axis. Treatment was begun on the fifth day. He was given fever induced by intravenous triple typhoid vaccine for three days, and after an interval of three days fever was induced twice more by means of blanketing and hot water bottles alone. Since his second reaction to vaccine had been poor, on the third day tight blanketing was used in addition to the vaccine, with the result that accidentally his temperature reached 109.8 F. He was cooled off from this very high fever quite rapidly by exposure alone, but his temperature was above 104 F for a total of about nine hours. Except for some vomiting, dehydration, and some acidosis he seemed to suffer no ill effects from this extreme hyperpyrexia. Following the first two fever treatments, there had been no change in the heart signs, but the third day following the temperature of 109.8 there was a striking change the rate was 80 there was no gallop the systolic murmur had lost its high pitched shrill, musical quality and the diastolic murmur was no longer heard. From then on no further signs of active carditis developed and tonsillectomy was performed three weeks after the end of treatment without exacerbation of activity in the heart. He was discharged with a diagnosis of enlarged heart and mitral insufficiency. During the two years since discharge he has had no chorea or other evidence of

SUMMARY TABLE OF THE SIXTEEN CASES OF CHOREA WITH CARDITIS

CASE	ADMISSION CARDIAC DIAGNOSIS	SIGNS OF ACTIVE CARDITIS	NO OF FEVER TREAT- MENTS	DAYS DURATION OF THERAPY	DURATION OF CLINICAL SIGNS OF CARDITIS
1	a. Rheum b. Acute carditis c. S T* d. E & F	Tachycardia Development of sys- tolic and diastolic murmurs under ob- servation	6	8	End of therapy rate slower, murmurs softer 10 days after end of therapy rate 78, S A present
2	a. Rheum b. E H, M I c. Acute carditis d. S T e. I	Fever on admission Tachycardia Gallop Quality of systolic murmur Presence of diastolic	6	8	End of therapy no gal- lop, rate 80, S A pres- ent 4 days later diastolic murmur no longer heard
3	a. Rheum b. Acute carditis c. S T d. E & F	Tachycardia Gallop Nodule High pitched, shrill, apical systolic mur- mur	14	26	4 days after beginning of treatment rate 80, S A present 6 days later no gallop, rate 80, no nodules. Systolic, soft and low pitched
4	a. Rheum b. E H, M I & S c. Acute carditis d. S T e. IIa	Fever on admission Tachycardia Gallop (present 2½ months before adm)	10	15	End of therapy no gal- lop, no tachycardia
5	a. Rheum b. E H, M I c. Acute carditis d. S T e. IIa	Fever Tachycardia Gallop Poor quality heart sounds Development of diastolic	6	6	End of therapy rate slower, gallop still present 5 weeks after end of therapy gallop gone.
6	a. Rheum b. E H, M I & S c. Acute carditis d. S T e. IIa	Fever Tachycardia Gallop Much accentuated P ₂ Prolonged P R inter- val	4	6	End of therapy no gal- lop, rate slow, P ₂ less loud, P R interval nor- mal
7	a. Rheum b. Acute carditis c. N S R d. F	Fever Development of Slight tachycardia Gallop Accentuated P ₂ Systolic murmur	7	7	2 days after end of ther- apy no gallop, rate slow
8	a. Rheum b. E H, M I c. Acute carditis d. S T e. IIa	Fever Tachycardia Gallop A V block (developed after treatment)	6	7	3 days after beginning of therapy no gallop, rate 100 End of therapy no gal- lop, rate 80

*Diagnoses were made according to the criteria for the classification and diagnosis of heart disease of the Heart Committee of the New York Tuberculosis and Health Association. Abbreviations used are: E. H. enlarged heart, M. I. mitral insufficiency, M. S. mitral stenosis, A. I. aortic insufficiency, A. S. aortic stenosis, N. S. R. normal sinus rhythm, S. A. sinus arrhythmia, S. T. sinus tachycardia, E.

I

TREATED BY ARTIFICIAL FEVER INDUCED BY TRIPLE TYPHOID VACCINE

COMMENT AND SUBSEQUENT COURSE IN HOSPITAL	COURSE SINCE DISCHARGE	DISCHARGE CARDIAC DIAGNOSIS	PRESENT CARDIAC DIAGNOSIS
0 weeks later erythema marginatum which persisted throughout stay No further signs of active carditis	Well for 16 mo when she developed indefinite signs of rheumatic activity	a. Rheum. b. M. I. & S. c. N. S. R. d. IIa	a. Rheum. b. E. H., M. I. & S. c. N. S. R. d. IIa
T & A. 1 mo after therapy with no exacerbation of rheumatic activity or of carditis	No evidence of rheumatic activity since discharge 11 mo ago	a. Rheum. b. E. H., M. I. c. N. S. R. d. I	a. Rheum. b. E. H., M. I. & S. c. N. S. R. d. I
Gallop reappeared for 10 days 1 month later with peridental abscess and fever T & A. done with no recurrence of carditis.	2 attacks of chorea, the 2nd accompanied by definite signs of carditis, since discharge 1 yr ago	a. Rheum. b. ---- c. N. S. R. d. E. & F	a. Rheum. b. ---- c. N. S. R. d. E. & F
No reappearance of signs of carditis.	Well for 1 yr In hospital at present time with signs of acute carditis.	a. Rheum. b. E. H., M. I. & S. c. N. S. R. d. IIa	a. Rheum. b. E. H., M. I. & S. c. Acute carditis d. S. T. IIa
Notes on chart poor Signs may have subsided earlier No other signs developed.	Questionable early signs of activity present 11 mo after discharge.	a. Rheum. b. E. H., M. I. & S. c. N. S. R. d. IIa	a. Rheum. b. E. H., M. I. & S. c. N. S. R. d. IIa
No further signs on this admission, but discharged too soon to the seashore.	Readmitted 2 mo later with chorea and signs of carditis. Admitted to hospital 8 mo later Died 3 wk. later with pericarditis congestive failure, acute nephritis.	a. Rheum. b. E. H., M. I. & S. c. N. S. R. d. IIa	Died
No further signs of carditis	No rheumatic activity since discharge 2 yr ago	a. Rheum. b. ---- c. N. S. R. d. E. & F	a. Rheum. b. ---- c. N. S. R. d. F
1 mo later Ekg showed A V block which persisted for 8 days, but with no clinical signs of activity Later T & A. done with no exacerbation.	2 subsequent attacks of polyarthritis at yearly intervals.	a. Rheum. b. E. H., M. I. & S. c. N. S. R. d. IIa	a. Rheum. b. E. H., M. I. & S. c. N. S. R. d. IIa

possible heart disease F potential heart disease I, functionally able to carry on normal activity IIa functionally able to carry on with slightly limited activity IIb, functionally able to carry on with markedly diminished activity III, signs of failure at rest in bed T & A., tonsillectomy and adenoidectomy

TABLE I

CASE	ADMISSION CARDIAC DIAGNOSIS	SIGNS OF ACTIVE CARDITIS	NO OF FEVER TREAT- MENTS	DAYS DURATION OF THERAPY	DURATION OF CLINICAL SIGNS OF CARDITIS
9	a. Rheum b Acute carditis c S T d E & F	Tachycardia Gallop Development of sys- tole murmur	7	8	After 1 fever no gallop, rate 100 End of therapy rate 88, murmur less loud 10 days later no mur- mur heard
10	a Rheum b Acute carditis c S T d E & F	Tachycardia Fever Accentuated P ₂ Development of dias- tole murmur	4	5	Rate slower at beginning of therapy End of therapy diastole murmur no longer heard
11	a Rheum b E H, M. I Acute carditis c S T d I or IIa	Tachycardia Gallop High pitched, shrill systole murmur Development of dias- tole murmur	6	8	End of therapy no gal- lop, rate 104, systole murmur still high pitched. 8 days later soft systole murmur, rate slow, S A present, short diastole
12	a. Rheum b Acute carditis c S T d E & F	Fever Tachycardia High pitched, shrill systole murmur No S A.	9	11	During therapy systole murmur became slight- ly softer 1 week after end of ther- apy systole murmur soft and low pitched, rate 100, S A
13	a. Rheum b Acute carditis c S T d E & F	Fever Tachycardia Gallop? Nodule? No S A. Development of dias- tole murmur	6	9	End of therapy rate 112, S A. present, no gallop, no nodule, no diastole murmur 1 week later rate 82
14	a Rheum b Acute carditis c S T d E & F	Fever Tachycardia Gallop Prolonged P R inter- val Development of dias- tole murmur	12	17	5 days after beginning of therapy rate 80 90, no gallop P R interval normal be- fore end of therapy
15	a Rheum b E H, M I c S T d IIa	Tachycardia Gallop Poor quality heart sounds	7	7	End of therapy rate 88, no gallop, sounds good quality, systole mur- mur softer
16	a Rheum. b E H, M. I Acute carditis c N S R d I	Gallop High pitched shrill systole murmur Presence of diastole	5	8	5 days after beginning of therapy no gallop, systole murmur soft and low pitched No diastole murmur heard

—CONT'D

COMMENT AND SUBSEQUENT COURSE IN HOSPITAL	COURSE SINCE DISCHARGE	DISCHARGE CARDIAC DIAGNOSIS	PRESENT CARDIAC DIAGNOSIS
No further signs of carditis.	4 months later chorea without carditis	a. Rheum. b. X ray E H c. N S R d. E & F	a. Rheum. b. ——— c. N S R. d. F
No further signs of carditis	1 subsequent attack mild chorea without signs of carditis, since discharge 16 mo ago	a. Rheum. b. — c. N S. R. d. E & F	a. Rheum. b. E. H. M. I. c. N S R d. I
Diastolic no longer heard 3 wk. later	No evidence of recurrence of rheumatism since discharge 1 yr ago	a. Rheum. b. E. H., M. I. c. N S. R. d. I	a. Rheum. b. — c. N S R. d. F
Taken home against advice 9 days after end of therapy. No signs of activity at that time.	Has not returned to clinic.	a. Rheum. b. — c. N S. R. d. E. & F	?
No further signs of carditis.	Did well for 6 mo after discharge then developed polyarthrititis, severe carditis and chorea.	a. Rheum. b. — c. N S. R. d. E. & F	a. Rheum. b. E. H., M. I. & S. c. S. T d. IIB
No further signs of carditis. Diastolic murmur gone 6 wk. after discharge	1 subsequent attack of chorea without carditis since discharge 15 mo. ago	a. Rheum. b. — c. N S R d. E. & F	a. Rheum. b. E. H. M. I. c. N S R d. I
Soft, late diastolic murmur heard from 1 wk. after therapy for about 10 days.	2 subsequent very mild attacks of chorea without carditis, since discharge 3½ yr ago.	a. Rheum. b. E. H., M. I. c. N S. R. d. I	a. Rheum. b. — c. N S R. d. E. & F
T & A 3 wk. after end of therapy with no exacerbation of carditis	No further evidence of rheumatic activity since discharge 2 yr ago	a. Rheum. b. E. H. M. I. c. N S R. d. I	a. Rheum. b. — c. N S R d. E. & F

rheumatic activity His general condition has been fairly good in spite of extremely low family income and bad hygienic care At the time of this report his heart showed no enlargement, but there was a moderately loud systolic murmur at the apex transmitted slightly toward the axilla

II FEVER THERAPY IN RHEUMATIC CARDITIS WITHOUT CHOREA

Because of the conclusion, which was almost forced upon us, that these children seemed to have benefited by their fever therapy as far as their hearts were concerned, it seemed justifiable to investigate the effects of fever on various forms of rheumatic heart disease without chorea

The most difficult type of child to handle therapeutically in the whole field of rheumatic infection is the child with evidence of subacute active rheumatic heart disease As a rule, he is not acutely ill, but the activity of his infection, as evidenced by low-grade fever, progressive weight loss, tachycardia, gallop, skin manifestations, etc., may continue for months even under the best of surroundings and produce severe crippling of the child's heart Up to the present time the only resources at our command for treating such a child have been elimination of foci of infection, prolonged rest in bed, high calorie and vitamin diet, and treatment of the usual anemia

Since we felt that children with certain forms of heart disease would be too sick to stand the foreign protein shock, inevitably occurring with fever produced by intravenous vaccine, we had an apparatus built in which fever is produced by radiant energy from carbon filament bulbs, after the specifications of Dr Stafford Warren, of Rochester University This is a box which fits over a bed and in it a child's temperature may be raised to any desired level, slowly or quickly, and maintained for as long a time as is necessary or the condition of the child allows The patients treated so far have been given a fever of approximately 106° F for from two to five hours

Up to the present time we have treated (1) five children with subacute carditis, four of whom received two treatments each, (2) one girl, fifteen years old, with subacute bacterial endocarditis on the basis of long-standing rheumatic heart disease, with neither harmful nor beneficial results, (3) one child with very severe acute rheumatic carditis, accompanied by polyarthritis and chorea, to whom we gave two fever treatments This child subsequently improved, but we were unable to say whether the fever therapy was a factor in the improvement

We are presenting in detail the first two cases treated which are the only ones that have been observed long enough to enable us to draw even tentative conclusions

CASE 1—L. B., seven and one half years old, was admitted Nov. 21, 1933, and was discharged June 29, 1934 She had had polyarthritis at five and six years of age and is said to have had heart disease since the age of three years The present illness began two weeks before admission with the development of an erythematous

rash. Three days later she began to feel tired and to have migratory joint pains and afternoon fever. On admission she appeared acutely and chronically ill, temperature was 101° F. there was a widespread erythema marginatum the heart was apparently enlarged there were tachycardia, presystolic gallop and accentuated P₂, a loud, harsh systolic murmur at the apex transmitted to the axilla and base and a low pitched apical diastolic murmur. White blood cells numbered 10,200 with 72 per cent polymorphonuclear leucocytes.

For the next ten weeks her condition remained about the same. Except for one period of nine days, her temperature was above 100° and sometimes 101° several times every week. In spite of complete rest in bed and extra nourishment, there was a progressive weight loss of 6 pounds. A widespread erythema marginatum was present most of the time. Tachycardia and gallop persisted. During the eighth week after admission rheumatic nodules were first noticed over both elbows and left external malleolus. The child continued to be listless and without appetite.

At the end of her eleventh week in the hospital she was given fever therapy by means of radiant energy for four hours, between 104° and 106°. During the treatment an extremely widespread erythema marginatum developed, which had disappeared by the next day. Following treatment her temperature remained consistently

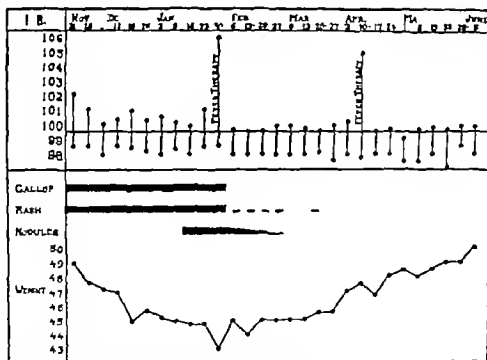


Chart 1 —(Case 1) Rheumatic carditis treated with fever produced by radiant energy. The temperatures indicated are the highest and lowest of a week.

below 100°. Her heart rate fell to normal, most strikingly shown is the drop in the sleeping pulse rate. her gallop disappeared. no occasional very small transient patch of erythema appeared but no further widespread erythema marginatum; no new nodules developed and those present gradually grew smaller and were not detectable in the fourth week after treatment. she immediately began slowly to gain weight. More striking even was the change in the child's general appearance and attitude. Within a week after treatment she had changed from a listless, lackadaisical child with a poor appetite, to a lively active one, bright and interested in her surroundings and with a ravenous appetite.

In the ninth week after treatment her temperature began to creep up above 100° and her sleeping pulse rate began to be slightly elevated. Therefore although her general condition continued to seem good and she was gaining weight it was decided to give her another fever treatment in the hope of nipping in the bud a fresh exacerbation of her rheumatic infection. She was given four and one-half hours at 104°. During the height of the fever a few small patches of erythema marginatum

became evident, in no way comparable to that of the previous treatment. During the two and one half months which she remained in the hospital following the second fever she continued to improve remarkably. Temperature and pulse remained normal, there was no further erythema of any sort, she continued to gain weight, more than regaining the six pounds she lost during the period before treatment. On discharge to a cardiac convalescent home no signs of activity could be detected, temperature and pulse were normal, white blood count and differential blood count and the erythrocyte sedimentation rate were normal.

CASE 2—M M, aged twelve years, was admitted Feb 21, 1934, and was discharged May 29, 1934. She had had repeated attacks of chorea, almost annually, since the age of four and one half years, but no other rheumatic history. We had followed her case since September, 1931, when she was treated with fever therapy for a moderate attack of chorea. Since that time she has had two very mild attacks of chorea, complicated by marked and definite habit spasms which were finally cured by psychotherapy. Her heart had never been enlarged, but there had been an apical

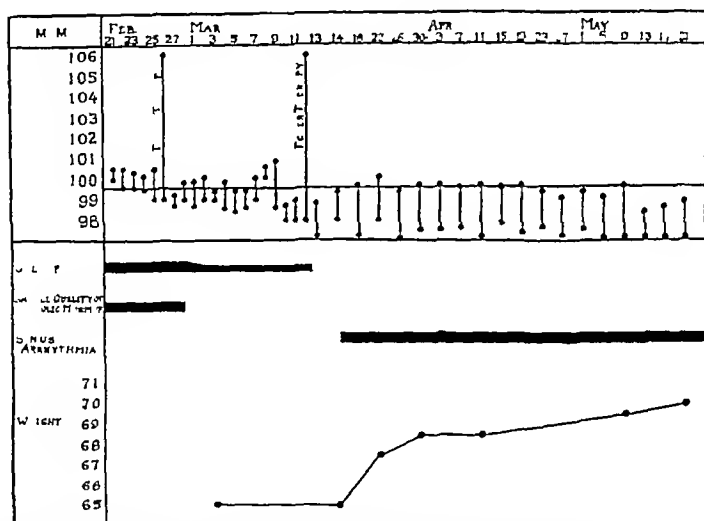


Chart 2—(Case 2) Rheumatic carditis treated with fever produced by radiant energy. The temperatures indicated are the daily highest and lowest for the first two weeks followed by the highest and lowest of four-day periods.

systolic murmur, transmitted slightly, present from the time of her first admission, and a diastolic murmur that had first been heard in December, 1932.

For two months previous to admission the mother had noticed tachycardia, dyspnea had developed when the child climbed one flight of stairs, and the child had been complaining of frequent precordial pain. Two weeks before admission she had had a sore throat and had been worse since that time. On admission her temperature was 100.4° F, heart rate was 130/140, there was a marked presystolic gallop, an apical systolic murmur with a high pitched, shrill, musical quality, and a short middiastolic murmur. No sinus arrhythmia was present. For the five days before treatment her temperature was above 100° every day, and the signs in her heart continued. In view of the observed tachycardia and precordial pain of two months' duration, she was thought to be a good candidate for fever treatment without further observation period in the hospital, on the sixth day she was given four hours of fever between 105° and 106° F by means of radiant energy. Following this her temperature was still somewhat elevated, but in general at a lower level, the gallop persisted but was definitely less marked, her pulse rate, although still

somewhat elevated, was slower than before treatment and the systolic murmur at the apex had lost its high pitched, musical quality. Although she was improved, there were still definite signs of activity. She was therefore given a second fever treatment two weeks after the first, her temperature being kept at 106° for three hours. Following this the gallop was no longer heard, her temperature remained normal, and her heart rate, although occasionally elevated during the day was consistently normal during sleep. The third day following treatment sinus arrhythmia was heard for the first time and persisted. Her general condition was much improved she had an excellent appetite and gained weight steadily.

As she had a gonorrheal vaginitis, she could not be sent to a convalescent home. However, shortly following her discharge three months after admission, she was taken by her mother to the seashore where she was active and without complaints. At her first return visit to clinic she had gained another pound in weight and showed no signs of rheumatic activity.

SUMMARY

1 Sixteen cases are presented in which the diagnosis of active rheumatic carditis was justified. The patients were given artificial fever therapy produced by the intravenous injection of triple typhoid vaccine, for a concurrent chorea.

2 In nine of these patients all clinical signs of activity had subsided by the end of treatment. In the others signs were gone in from a week to ten days following the end of treatment.

3 Two cases are presented of subacute rheumatic carditis without chorea. The patients were given artificial fever therapy produced by radiant energy.

4 In one patient the signs of rheumatic activity cleared immediately following one treatment but recurred again to a much lesser degree eight weeks later. She was given a second fever treatment and has shown no clinical evidence of activity since.

5 The second patient improved following one treatment, but the signs of activity did not completely subside until after a second treatment two weeks after the first.

CONCLUSIONS

1. We believe that artificial fever therapy produced by the intravenous injection of triple typhoid vaccine or by radiant energy had no harmful effects on the course of the carditis in these children.

2 Furthermore, the application of the fever therapy seemed to have a beneficial influence on the course of the carditis.

3 The presence of a subacute carditis or of inactive rheumatic heart disease is not necessarily a contraindication to the use of fever therapy in the treating of chorea.

4 We suggest that the use of fever therapy in forms of rheumatic fever other than chorea deserves further study.

168 EAST SEVENTY FOURTH STREET

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VIRUS ENCEPHALITIS

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MOST of the cases of postvaccination encephalitis are reported from Europe. So recently has Newman¹ collected the reported cases here and abroad that repetition is not justified. The scant number of American cases finding their way into literature, seventy-four in all, justifies the following case report.

H. M. G., female, aged six years, was vaccinated by her family physician preparatory to going to school. Ten days later she became very drowsy, complained of headache, ran a temperature of 102° F., and later in the day had a convulsion which lasted one half hour. When she recovered from the convulsion, she was stuporous and her temperature continued to rise. The following day she was admitted to St. Christopher's Hospital in convulsions with a temperature of 104° F. At that time her neck was slightly rigid, and her head was turned stiffly to the left. The eyes were open, and the pupils were dilated. They did not react to light. Ophthalmoscopic examination showed a marked venous tortuosity in both eyes. All of the extremities were spastic, and the reflexes were exaggerated, but at the time no Kernig, Babinski, or Oppenheim signs, or ankle clonus were present.

On the left arm there was a vaccination that was clean and healthy, typical of a ten to twelve day mark. No other physical findings of importance were noted. After this convulsion which was followed by several minor ones, she was in a state of coma which lasted for three days in all. Vomiting occurred frequently during the first four days in the hospital. The temperature remained between 103° and 104.3° F.

The cerebrospinal fluid pressure registered 20 mm., specimens having 50 to 55 cells, polymorphonuclears predominating. Sugar was present, and globulin was increased. The blood count showed a slight leucocytosis and the differential ratio was normal. During the comatose state fleeting positive Babinski signs and ankle clonus were noted.

On the sixth day of illness the child recovered consciousness and recognized her mother. The temperature started to come down and in five days was normal. From then on the convalescence was uninterrupted. No mental or nervous changes occurred. Two years later she was robust and mentally clear and alert. There were no behavior changes.

The vaccination ran a normal course never showing any unusual inflammation or infection. The scar can be completely covered with a ten cent piece. The denudation method was employed. Incidentally, she had had no previous immunizing agent.

COMMENT

Postvaccination encephalitis is pathologically different from epidemic encephalitis. Flexner² calls attention to the difference in histopathology that can be summed up in the following

From the Jefferson Medical College.

Postvaccination encephalitis shows adventitial and periadventitial round cell infiltrations distributed throughout the brain and cord. Myelin degeneration which gradually fades into normal myelin structure may be seen about smaller vessels. The characteristic softening or microglia proliferation about the blood vessels of the white substance of the central nervous system resembles the action of a toxic substance. Epidemic encephalitis is proliferative and infiltrative. The lesions are almost always confined to the brain and chiefly to the basal gray matter. Lymphocytes are found in layers in the perivascular lymph spaces. Postvaccination encephalitis is more widespread, is unevenly distributed and is more partial to white matter.

Clinically, postvaccination encephalitis is marked by the triad of headache, vomiting, and pyrexia, at the onset followed by rigidity of the neck, coma, and in many cases, convulsions. Temporary paralysis is insisted upon by English writers as an accompaniment. The course is stormy and alarming from the outset and the prognosis is grave. The vaccination shows no deviation from the usual picture of a "take" but it does not have to be a successful vaccination to be responsible for the syndrome under discussion. When not fatal complete recovery mentally and physically takes place. This is very surprising in view of the above pathologic picture as presented by the fatal cases.

So much emphasis has been laid upon the differentiation between postvaccination encephalitis and epidemic encephalitis that but scant attention has been given to a comparison between postvaccination encephalitis and the encephalides following the acute exanthemas and a few other infections.

Encephalitis following measles has been reported by Musser and Hauser,³ Ferraro and Scheffer,⁴ and others. This encephalitis occurs during or shortly after the attack of measles. Clinically the signs and symptoms as described by these authors are identical with the picture of postvaccination encephalitis as portrayed above. With but very slight difference in the extent of cord involvement, the pathology is also similar in the two conditions. In fact the descriptions of Flexner's postvaccination encephalitis and Musser and Hauser's and Ferraro and Scheffer's postmeasles encephalitis are strikingly similar and their published microscopic pictures emphasize the closeness of the relationship between these conditions, but none call attention to it.

Flexner's observation noted above assumes added significance therefore when he states that the lesion of postvaccination encephalitis is typical of the action of some toxic substance. Since virus has been recovered in the cerebrospinal fluid in the postvaccination encephalitis and not in the vaccinated who do not suffer with encephalitis, it might be fair to assume that the toxic substance is a virus. That there is a relationship between the virus of postvaccination encephalitis and the virus of postmeasles encephalitis is strongly upheld by Armstrong.⁵

Encephalitis is quoted as a complication of varicella and variola by practically all of the recent textbooks but no clinical picture is presented. Appended is a case that can with propriety be classed in this category.

Patient R. K., seven year old boy, developed fever, delirium, and vomiting ten days after the onset of varicella. He complained of headache. In forty eight hours he became stuporous, then comatose with convulsive tremors. This persisted for three more days after which he recovered consciousness. He had had measles, mumps, and pertussis. He has never been protected against diphtheria nor vaccinated.

This case came under the observation of Dr. M. M. Bekir on the third day of the encephalitis, who called me to see the child on the fourth day at Memorial Hospital, Roxboro. At that time physically the patient presented these salient findings. The eyegrounds showed some venous engorgement. He had a rigid neck, a positive Kernig sign, an exaggeration of all reflexes, and a positive Babinski sign. There were convulsive movements of all extremities, athetoid in type. A temperature of 103° F. persisted for one week. The spinal and cisternal tap showed a clear fluid under pressure, averaging from sixty to eighty cells, with polymorphonuclear cells predominating. Sugar was reduced, globulin increased. His blood counts showed a secondary anemia and the white blood count averaged sixteen thousand with 87 per cent polymorphonuclears, 12 per cent small mononuclears, and 1 per cent eosinophiles.

He made an uneventful recovery, and his mental faculties seem unimpaired. However, but one year has elapsed since his illness.

Note the similarity between this case and the case of postvaccination encephalitis and the tendency to some meningeal irritation as it obtrudes itself upon the pictures.

Since both of these children reported recovered, demonstration of their pathologic lesions is impossible. It is at least evident that virus infections can, and do, produce encephalitis that differs from the type of encephalitis known as "epidemic encephalitis" or "encephalitis lethargica." There is also a close bond between virus-produced encephalides despite the marked difference in the clinical pictures of vaccination, smallpox, measles, chickenpox, and scarlet fever.

It is presumed as before stated that vaccine virus is the etiologic factor in postvaccination encephalitis because the virus has been recovered from the cerebrospinal fluid. This would lead to the presumption that similar viruses operate to produce the similar clinicopathologic pictures in the other encephalides that sometimes accompany the exanthemas. Indeed it might even argue for the virus etiology of scarlet fever. However, this is not complete proof.

It might also be assumed that a usually innocuous virus is rendered virulent by any one of the viruses causing any one of the exanthemas. Gorter,⁶ of Leyden, supports this view. He agrees with Bok of his own country that the virus encephalides are all one and the same disease due to the activation of the ordinarily innocuous virus. He states that in the Netherlands they have rarely recovered vaccine virus from the cere

hospital fluid in postvaccination encephalitis. The German authorities, however, assert that they have recovered it in a high percentage of cases. This is possibly a technical discrepancy.

Pleomorphic streptococci, protozoa, and yeasts are assumed to be activated by virus. The almost omnipresence of streptococci in health or disease has certainly given it the distinction of causing a multitude of diseases of which it is probably primarily innocent. The actual etiologic factor is still open to argumentation for final scientific solution.

Despite the lack of definite information concerning etiology, it is presumed to offer preventive measures against postvaccination encephalitis, but the other virus encephalides are still elusive. Empirical as they are, a few prophylactic rules may be productive of successful results. These rules are based on sound clinical observation. Clinical observation, after all, needs no apology made for it.

First, the rarity of postvaccination encephalitis following vaccination in infants under one year of age cannot be explained away by the statement that fewer children are vaccinated at that age than at a later period in life. That infants are not apt to be sensitive to virus in these early months of life is generally accepted. The same holds true of secondary vaccinations at any age. Couple this with the advantage of more careful attention to wounds in infants as compared with the dangers of contamination and dirt in the preschool age group, and there is a potent argument for early vaccination.

Second if the infant has been further desensitized to virus by other immunizing agents notably diphtheria toxoid, it has even less chance of developing encephalitis. This must be noted however that vaccination performed too soon after the toxoid injection will probably not be successful. Particularly is this true of alum precipitated toxoid. Allow at least a month to elapse after diphtheria immunization before vaccinating.

Third the single slight one eighth inch scratch or puncture method should be the procedure employed in performing the vaccination. Only healthy children should be vaccinated. The multiple scratch multiple puncture, or denudation method allow relatively large quantities of virus access to the patient, whereas the recommended procedure allows but little. Particularly is this true if the virus is rubbed into the scratch only until the edges of the scratch become ischemic and the residue of vaccine wiped off completely with sterile cotton. It has been shown that while virus multiplies in the human, this small amount takes sufficient time to catch up to the larger amounts and desensitizes individuals before it reaches the maximum of the large dose administered.

The probable relationship of the encephalides enumerated in this discussion demands the closest scrutiny. Their tendency to occur in the

lymphatic types and the more robust subjects may complicate the study, but it does point to virus implication since the virus multiplies in these subjects more rapidly than in their opposites

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345 SOUTH NINETEENTH STREET

SOY BEAN (VEGETABLE) MILK IN INFANT FEEDING

RESULTS OF THREE AND ONE HALF YEARS STUDY ON THE GROWTH AND DEVELOPMENT OF 205 INFANTS

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IN December 1932¹ we published a preliminary report on the results obtained with fifty infants who were fed soy bean milk for a period of six months or longer.

Up to that time we had been using a flour made from the Mammoth Yellow beans, to which were added malt syrup, lactose cottonseed oil, calcium and magnesium lactate the chlorides of sodium and potassium, and the glycerophosphates of iron and calcium butter fat and cod liver oil. These additions were made because of certain deficiencies in the bean itself, notably mineral salts and carbohydrate. A study of the vitamin potency of the flour indicated that the quantities of vitamins A, D, and B complex in the mixture were adequate for the normal growth of rats.

The composition of the flour plus the above additions, was as follows:

	Percentage
Moisture	2.50
Protein	28.69
Fat	20.20
Carbohydrate	48.81
Total ash	5.30
Starch	0.50
pH	5.50 (reliquefied)

One ounce of this powder equaled 125 calories. Reliquefied, in the proportions of 35 gm. of the powder to 8 ounces (236 c.c.) of boiled water gave the following formula:

	Percentage
Protein	3.60
Fat	3.07
Carbohydrate	7.30

(One ounce equals approximately 194 calories.)

The infants were studied in two groups (1) breast fed babies receiving an insufficient quantity and (2) babies fed exclusively on soy bean milk.

An analysis of the composite and individual weight charts at that time indicated that the majority of the infants did well making good average gains and developing normally.

¹From the Pediatric Service of St. Ann's Hospital and the Out Patient Pediatric Clinic of St. Luke's Hospital.

Since publication of this preliminary report we have made several changes in the composition of the original soy bean formula. The chief changes were made in the protein-carbohydrate ratio since it was thought that the protein percentage in the original formula was proportionately high. The final formula, designated as soy bean E, and which we have used for the past two years, has the following composition:

	Percentage
Protein	14.00
Lactose	53.00
Fats (cottonseed, butter, etc.)	17.80
Ash	5.00
Moisture	2.50
Iron (as metal)	0.0142
Calcium	0.80
Phosphorus	0.50

Rebquefied, in the proportions of 35 gm. of the powder made to 8 ounces with water, the formula gives protein, 2.12 per cent, fat, 2.71 per cent, carbohydrate, 8.00 per cent, with a calorie equivalent of 19.6 to the ounce. This gives approximately a 4:1 ratio of carbohydrate to protein.

Over two hundred infants were observed while receiving this "milk" and their respective weights and development noted. An analysis of the results in feeding this preparation demonstrates its superiority over the original formula. (Charts 1 and 2)

SOY BEAN AND SKIMMED MILK

There are several varieties of the soy bean (Mammoth Yellow, Manchu, Illinois, etc.) which differ in their relative proportions of the amino acids, notably tryptophane, lysine, etc. It was thought, therefore, that the bean flour in combination with skimmed milk might yield improved growth factors because of the vegetable-animal protein combination, plus a fortified amino acid constituency. Accordingly, we prepared two formulas known as SW and SSW, the S and SS signifying the skimmed milk protein added, the W indicating a wheat germ addition for the vitamin B complex.

	Soy Bean SW (Percentage)	Soy Bean SSW (Percentage)
Protein (soy bean)	11.00	7.00
Protein (skimmed milk)	3.00	7.00
Lactose	53.00	53.00
Fats	17.80	17.80
Ash	5.00	5.00
Moisture	2.50	2.50
Iron (as metal)	0.0142	0.0142
Calcium	0.50	0.50
Phosphorus	0.17	0.13

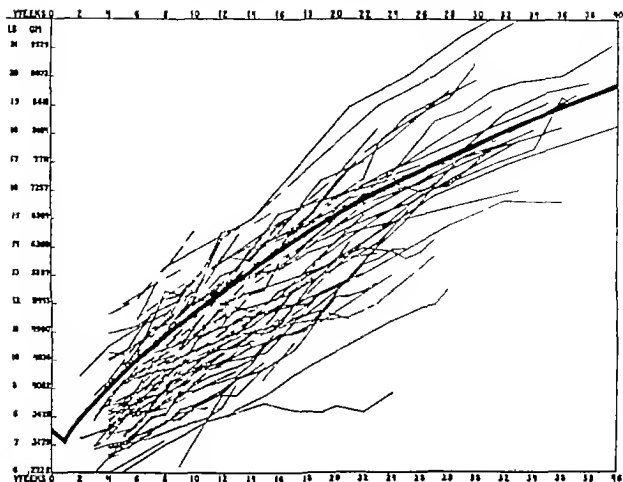


Chart 1—Eighty four infants on breast feeding plus soy bean milk E plain

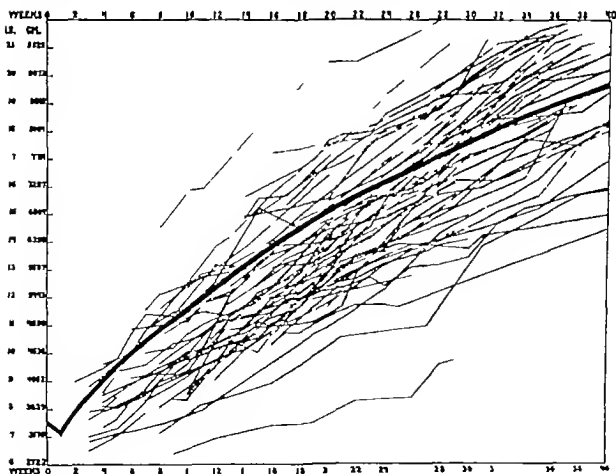


Chart 2—Sixty nine infants on soy bean milk plain only

From these formulas it will be seen that the chief difference lies in the protein percentages of the added skimmed milk. Charts 3 and 4 show the weight curves of fifty-two infants fed on the soy bean-skimmed milk preparations, twenty-seven of whom received additional breast milk. While there is no apparent, marked difference as compared with the babies fed on the plain soy bean preparation, we felt, nevertheless, that the combined proteins afforded a definitely reinforced, prophylactic soy bean food. Tso² has demonstrated that it requires a higher protein caloric intake of the soy bean to equal the nutritive properties of a cow's milk protein-caloric intake in lower proportion. It would seem, therefore, that a combination of the two types of protein offers a distinct advantage from the standpoint of nutrition and growth.

VITAMIN POTENCY

A complete vitamin assay was included in our preliminary report, which showed that the preparation contained an adequate amount of the A, B and D complexes. The introduction of wheat germ in the new formulas was made for the purpose of increasing the B complex. Vitamin D potency is further fortified by including cod liver oil in the soy bean flour mixture.

METABOLISM STUDIES

Nitrogen—During the past few years investigators have reported careful studies on the nitrogen metabolism of infants fed on soy bean protein.^{3 4 5 6} In these investigations different soy bean preparations were used, varying from the ground whole bean to water-soluble fractions of the bean as the source of protein. In addition, various percentages of soy bean protein were fed with a view to determining the ability of the infant to utilize the vegetable protein.

Our investigations were undertaken in order to determine the retention of nitrogen by the infants fed on our soy bean preparations, namely, soy bean E (plain), SW, and SSW.

The infants, seven in number, were selected from those coming regularly to the dispensary and had been fed exclusively on one of the soy bean preparations for some time prior to admission to the hospital. They were placed on a canvas bed strapped at the four corners to the upright supports of the crib and strapped to the canvas, the buttocks resting on a padded rim of an aperture cut in the canvas support. A stool pan was held in place beneath the buttocks and a special tube was attached to the infant for the collection of urine.

A sample of food sufficient for the entire experiment was thoroughly mixed and daily portions weighed from this sample. In this way it was possible to determine accurately how much nitrogen, calcium, and phosphorus were provided in the quantity given to the baby. Any portion of the food refused was measured and proper allowance made.

The infants were kept on the metabolism bed for a total of four days, during which twenty-four hour collections of the urine and feces were made. The samples were thoroughly mixed and portions for analysis taken. Nitrogen was determined by the Kjeldahl sulphuric acid method with copper sulphate as the catalyst.

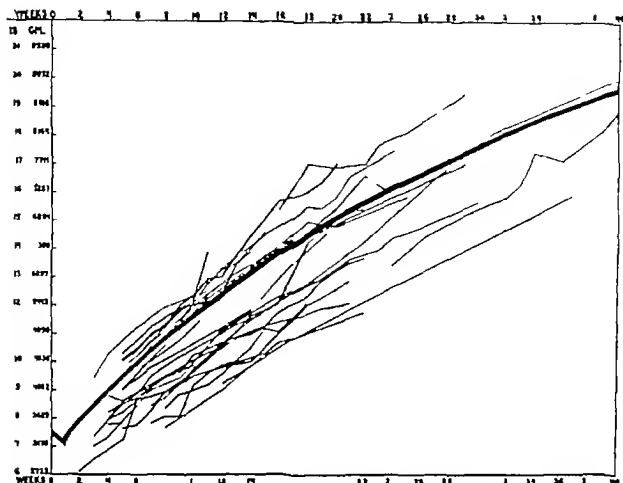


Chart 3—Twenty-seven infants on breast feeding plus soy bean milks S or SSV

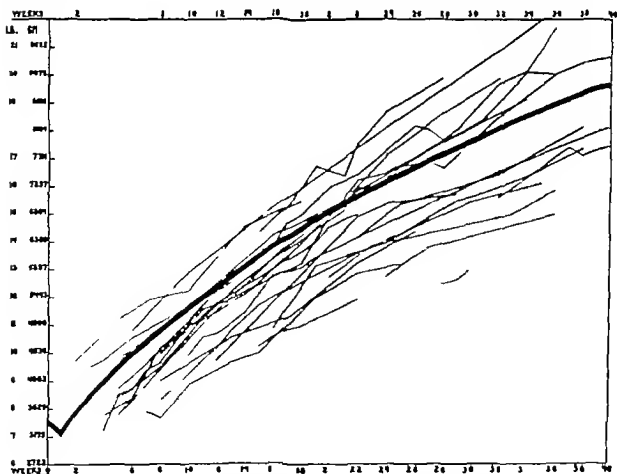


Chart 4—Twenty five infants fed soy bean milks S and SSV

The infants varied in weight from 2,800 to 7,650 gm. They were fed the particular soy bean preparation under investigation, the protein calories varying from 11.8 per cent to 15.8 per cent. Exact analysis of each sample fed to the individual infant showed slight variations in the composition. Infant C—r was fed each of the three different formulas (E, SW, SSW) so that exact comparison with the same system and conditions is possible. All the infants were offered liberal feedings, depending on appetite and tolerance, and were fed at four-hour intervals. The caloric intake varied from 70 to 217 per kilogram.

The fresh weight of the stools varied somewhat but averaged 470 gm for the period of the investigation. This is somewhat higher than the figure reported by Tso and Chu,⁵ whose average for the same period was 215 gm. This might be accounted for by the fact that our preparations were made from the whole bean while Tso used only a portion of it. The stools are usually very soft and moist. One analysis showed less than 20 per cent solids.

The nitrogen intake was higher in the case of Baby McN—l and lower in the case of Baby M—a, who ate less food and was a rather poorly nourished infant of a neuropathic constitution (Table I).

TABLE I

INFANT	BODY WT IN GM	CAL- ORIES PER KG	PROTEIN CAL (PER CENTAGE)	NITRO- GEN INTAKE IN GM	RETEN- TION OF N GM	GM /KG	UTILIZA- TION PER CENTAGE	RE- TENTION PER CENTAGE
H—i	7,650	70.0	15.8	3.525	0.665	0.085	80.5	14.4
McN—l	4,200	200.0	15.8	4.353	1.800	0.428	81.6	41.0
B—k (1)	2,800	217.0	15.8	3.880	2.648	0.946	---	69.1
B—k (2)	3,175	146.0	15.8	2.955	1.550	0.490	70.0	52.0
C—n E	3,940	108.0	13.0	2.320	0.757	0.192	78.5	32.2
J—e (SW)	3,770	112.0	14.5	2.391	0.895	0.237	66.0	37.4
C—r (SSW)	4,890	140.0	13.7	3.510	1.340	0.274	83.4	38.2
C—r (SW)	5,200	117.0	14.0	3.218	1.080	0.208	83.6	38.9
C—r (W)	5,250	114.0	11.8	2.755	0.624	0.120	70.0	23.0
M—a (SSW)	5,740	70.0	13.7	2.106	0.827	0.144	78.5	39.3

The utilization varied from 66 to 83 per cent, which compares favorably with other reports. The retention varied from 14.4 to 69.1 per cent. The very high retention in the case of Baby B—k (1) can probably be explained on the basis that the intake of nitrogen was very high during the period of study. This baby was premature, and therefore does not give a true index of the retention on this particular soy bean preparation. In general it can safely be stated from the results of this study that at a protein-calorie intake of approximately 13 per cent, the percentage of nitrogen retention is at a level approximating that of similar cow's milk feeding. Summarizing, then, the results of these metabolic investigations, we find:

1. At a protein-calorie level ranging from 11.8 to 15.8 the level of nitrogen retention was fairly high, varying from 14.4 to 69.0 per cent.

2 An arbitrary level for protein calories in the diet has been established at approximately 140 per cent

3 Either plain soy bean milk or soy bean milk combined with skimmed cow's milk gives adequate retention of nitrogen when fed to infants

Calcium and Phosphorus—The calcium and phosphorus utilization was observed for five of the metabolism periods during which nitrogen balance was determined, the infants receiving the diet for considerable periods before being placed on the metabolism bed. Calcium was determined by the Shohl-Pedley method, and phosphorus by the colorimetric method of Benedict and Tice. Table II shows the results of these investigations.

TABLE II

INFANT	CALCIUM				PHOSPHORUS				Ca P Ratio
	IN TAKE GM	RE TEN TION GIL	GM/KG	PER CENT- AGE	IN TAKE GM	RE TEN TION GIL	GM/KG	PER CENT- AGE	
J—e (SW)	0.638	0.378	0.100	60	0.132	0.049	0.013	37	7.5:1
C—r (SSW)	0.812	0.272	0.058	38	0.270	0.151	0.031	56	2.0:1
C—r (SW)	0.702	0.363	0.070	51	0.238	0.155	0.030	63	2.3:1
C—r (W)	0.910	0.384	0.074	42	0.229	0.130	0.025	60	3.0:1
M—a (SSW)	0.496	0.214	0.037	43	0.100	0.092	0.017	53	2.2:1

The authors wish to acknowledge the assistance of Miss Carla Zorn who performed the necessary analyses for the calcium and phosphorus studies.

The results in Tables I and II show a very satisfactory retention of all three elements, nitrogen, calcium and phosphorus. This is especially of interest in view of the diversity of the amounts of each element fed. The only exceptions are the phosphorus values for Babies J—e and M—a whose intakes were also very low. In all cases the phosphorus figure falls considerably below the amount that should be retained in order to fulfill the requirements given by Stearns.⁷ About the same results were found by Tso, Yee and Chen,⁸ and by Stearns⁹ in their experiments with soy bean milk feeding.

Shohl and others¹ have indicated that the ratio of calcium to phosphorus should be approximately 6:4 for proper growth of bone and to supply phosphorus for tissue development. The above figures for retentions showing 2:1 and 3:1 ratios would therefore be much too high in calcium. This deficiency does not show up in the values for serum calcium and phosphorus given elsewhere in this paper, a result which corresponds to the findings of these authors, namely, that the body composition remains normal and the lack of phosphorus results only in retarded growth.

BLOOD STUDIES

Blood counts were made on a number of the infants; the average red cell count was 4,920,000, while the hemoglobin gave a good average of 13.9 gm per 100 cc (Newcomer).

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The utilization varied from 66 to 83 per cent, which compares favorably with other reports. The retention varied from 14.4 to 69.1 per cent. The very high retention in the case of Baby B—k (1) can probably be explained on the basis that the intake of nitrogen was very high during the period of study. This baby was premature, and therefore does not give a true index of the retention on this particular soy bean preparation. In general it can safely be stated from the results of this study that at a protein-caloric intake of approximately 13 per cent, the percentage of nitrogen retention is at a level approximating that of similar cow's milk feeding. Summarizing, then, the results of these metabolic investigations, we find

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of bile pigments since the stools gave a positive Gmelin test. Ether extraction showed some greenish coloration. No fat or free starch were found. Pea-sized pieces of each of the nine stools were emulsified in 2 c.c. of sterile physiologic salt solution. The emulsions, to which a few glass beads were added, were then vigorously shaken by means of a Wright eccentric hand centrifuge, and two standard loopfuls of each emulsion were smeared on each of the two slides. The slides were air dried, fixed by heat, and stained by the Jensen-Gram method. A total of 500 organisms covering several fields of both slides were counted.⁷

From the results (Table III) it is clearly evident that with the exception of stool 5 the stools were composed of a high percentage of gram positive organisms. Stools 2, 3, 4, and 6 gave a fairly high percentage of probable *B. bifidus-acidophilus* forms.

TABLE III

STOOL NO	GRAM NEGATIVE ORGANISMS (PER CENTAGE)	GRAM POSITIVE ORGANISMS (PER CENTAGE)	COCCI ALL FORMS (PER CENTAGE)	GRAM POSITIVE RODS (PER CENTAGE)	SLENDER AND SLIGHTLY CURVED GRAM POSITIVE RODS <i>B. BIFIDUS-ACIDOPHILUS</i> (PERCENTAGE)
1	+ 20	+ 80	+ 10	+ 70	+ 6
2	+ 18	+ 82	+ 16	+ 66	+ 23
3	+ 5	+ 95	+ 84	+ 61	+ 18
4	+ 18	+ 87	+ 24	+ 63	+ 24
5	+ 64	+ 86	+ 8	+ 28	+ 4
6	+ 6	+ 94	+ 10	+ 84	+ 29
7	+ 28	+ 72	+ 43	+ 29	+ 9
8	+ 17	+ 83	+ 22	+ 61	+ 5
9	+ 20	+ 80	+ 7	+ 78	+ 8

ROENTGENOLOGIC STUDY

X ray studies of the long bones were made of eighteen infants. These were checked for bone development and bone texture by Dr. Francis of the Brush Foundation. The results are shown in Table IV. The great majority of these showed good bony development and good texture with no signs of rickets. In a few instances the pictures revealed suspicious evidence of rachitic changes, yet the serum calcium and phosphorus were well within the normal limits and clinical signs were lacking.

DIGESTIBILITY AND BUFFER ACTION

That the protein of soy bean milk compares favorably with that of cow's milk from the standpoint of digestibility has been demonstrated by Adolph and Wang.¹⁰ These investigators conducted a series of tests in vitro, the results showing that peptic digestion was greater for the soy bean milk than for cow's milk. This they attribute to the possibility of different linkages or to the fact that no hard curd is formed by acid. The optimal pH was identical for both at 1.66. The percentage of digestion was 57.6 for soy bean milk and 37.8 for cow's milk.

Experiments with trypsin revealed a greater digestibility, at the optimum pH, for cow's milk. Tryptic digestion was 61 per cent for soy bean milk at a pH of 10.2, while for cow's milk the percentage of digestion was 78 at a pH of 11.3. Experiments in vivo (rats) on a ten-day test showed the digestion of the soy bean milk to be about 84.9 per cent, while for cow's milk the average was 86.6.

Reid¹¹ conducted some experiments on a soy bean milk-egg preparation. He removed the husks from soaked beans, which were ground and filtered through cloth. This was boiled for fifteen minutes. Fifty grams of cane sugar, plus 30 gm. of egg yolk, 1 gm. of sodium chloride, and 2.5 gm. of calcium lactate were then added to each liter and the entire

TABLE IV

INFANT	AGE IN MO	ROENTGENOGRAM		
D H	10	B.D.,* 9 mo	B T,† fair	No rickets
S W	9	B.D., 9 mo	B T, light	No rickets
A G	9	B D, 5 mo	B T, light	Rickets suspected
G R	8	B D, 5 mo	B T, good	No rickets
J B	6	B D, 3 mo	B T, poor	Rickets suspected
R P	12	B D, 10 mo	B T, light	No rickets.
D N	11	B D, 5 mo	B T, good	No rickets
R E	10	B D, 3 mo	B T, good	No rickets
R. B	8	B.D., 5 mo	B T, good	No rickets
S H	8	B.D., 9 mo	B T, fair	No rickets
E Q	8	B D, 3 mo	B T, light	Rickets suspected
EM	10	B D, 9 mo	B T, good	No rickets.
J H	8	B.D., 3 mo	B T, good	No rickets.
C M	12	B.D., 18 mo	B T, light	No rickets.
J Z	12	B D, 5 mo	B T, fair	No rickets.
G M	7	B D, 2 mo	B T, good	No rickets.
F R	10	B.D., 5 mo	B T, fair	No rickets.
D H	11	B D, 3 mo	B T, good	No rickets

*B D bone development.

†B T bone texture

mixture spray-dried at 50 to 55° C. Peptic digestion in vitro showed boiled cow's milk and boiled, reconstituted soy egg milk equally digestible. At an acidity over 0.13 per cent of HCl, raw cow's milk was more digestible. Raw cow's milk was 25 per cent less digestible than the boiled, while raw soy egg milk was 50 per cent less. Tryptic digestion showed that boiled cow's milk digestion is much higher than either the raw cow's milk or soy-egg milk.

Chart 5 illustrates the buffer curves for the three preparations of soy bean milk (SW, SSW, and E). The acidity was determined by the quinhydrone electrode. It will be seen that the curves for the SW and E parallel each other closely up to the point where 20 cc of 0.2 N HCl was used. There is a greater divergence of the curve for the SSW preparation.

SOY BEAN MILK AND INFANTILE ECZEMA

In a previous communication¹² we reported on the results obtained in a small series of cases of infantile eczema using the soy bean milk (E) as a dietary method of therapy. The rationale was based on the substitution of a vegetable protein for the animal protein of cow's milk, on the premise that the skin manifestations were due to sensitization to animal protein. This theory and the subsequent use of soy bean milk as a dietetic cure was first suggested by Hill and Stuart.¹³ Our results were for the most part good. However, it has been our experience that in a few instances, in spite of the fact that the causal factor points to a milk sensitization we have been unable to clear the eczematous lesions by the substitution of soy bean milk.

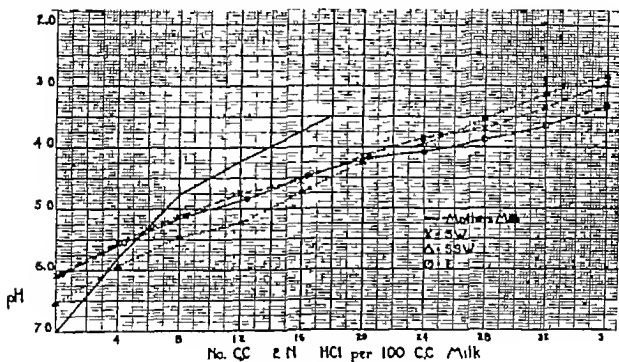


Chart 5—Buffer curves for various milks.

Recent investigations by other workers have brought to light some interesting data on the question of the etiology of infantile eczema. It further suggests a possible explanation for the beneficial results obtained with soy bean feeding other than that based on the protein.

Shortly after our paper was submitted for publication¹² there appeared in the literature a very interesting series of reports by Hansen,¹⁴ and Hansen and Burr¹⁵ on the possible explanation of the etiology of infantile eczema. Burr and Burr¹⁶ found that rats underwent marked skin changes when suffering from unsaturated fatty acid deficiency disease. This suggested that some dermatologic disorders of childhood such as eczema, might be dependent on this dietary deficiency.

Hansen determined the iodine absorption number in ten cases of infantile eczema and in sixteen normal infants. This was followed by the determination of the total fatty acids, cholesterol total iodine absorp

tion of the serum, and the iodine number of the serum fatty acids in five normal and six eczematous infants. In the eczematous infants the average I A N (iodine absorption number) was 383, while the controls averaged 539. He found that the iodine number of the serum fatty acids was abnormally low in infantile eczema during the active phase of the disease. Twenty-one determinations on eleven cases of eczema showed the average iodine number to be 82, as against 114 for the controls.

On the basis of these findings, he treated a series of cases of eczema by the administration of oils rich in unsaturated fatty acids. The diet and local treatment were the same for all. Out of a group of four infants, one was used as a control, the remaining three infants receiving supplements of linseed or corn oil. The iodine number of the serum fatty acids was subnormal in all four cases before treatment but increased to normal levels with marked improvement in the skin condition. The control infant, receiving no oil, failed to show definite clinical improvement, and the iodine number did not rise.

Further studies on the iodine absorption of serum in rats fed on fat-free diets revealed a low index, the highest iodine absorption of the "fat-free" animals being lower than the lowest I A N of the control rats. The cholesterol and total fatty acids of the serum were also much lower in the rats on the fat-free diet.

It is obvious that further work along these lines must be done before we can draw conclusions as to its importance and significance in the matter of etiology. However, these investigators deserve a vote of thanks from pediatricists for what promises to lead us into an effective line of therapy.

The importance of their investigations from the standpoint of soy bean milk feeding lies in the relatively high proportion of the unsaturated fatty acids in soy bean oil. On the basis of their findings the question arises as to what factors are operative in the clearing of eczematous lesions by means of soy bean milk feeding. Are the beneficial results due to the substitution of the vegetable protein or to the unsaturated fatty acids in the soy bean oil?

The work of Hansen and Burr thus opens a new line of investigation, namely, the therapeutic effects of the administration of soy bean oil as compared with linseed and corn oil. It is our intention to apply this form of therapy to a series of cases of infantile eczema with the hope of being able to contribute some informative data.

CLINICAL RESULTS

The earliest age at which soy bean milk was started was two weeks. All infants were given supplementary doses (daily) of cod liver oil, averaging from 1 to 2 teaspoonfuls. Orange juice was, of course, included.

One group was started on food supplements (cereals and vegetable pulp) at three months, while the remaining groups were started at six months.

Chart 1 is a composite picture of the weight curves in a series of eighty four infants fed on the plain soy bean milk with variable quantities of breast milk. As will be noted the curves parallel the Holt line for the most part. A few show sharp breaks with a tendency to flattening. Several curves are broken by plateaus. Many of these occurred as a result of intercurrent infections. In a few instances we were

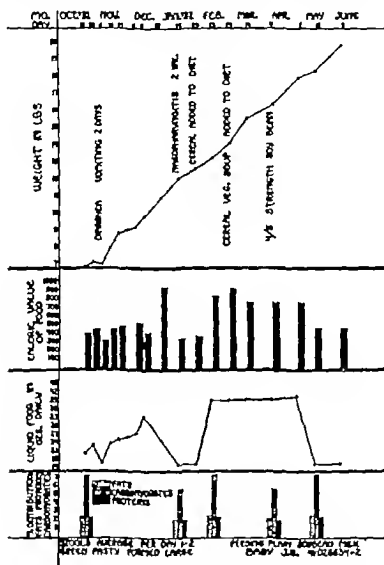


Chart 5.

unable to account for the poor gains. However the composite curve compares favorably with similar curves from infants fed on cow's milk preparations.

Chart 6 is a representative, individual picture of progressive gains over a period of seven months on the plain soy bean milk feeding. It is interesting to note that in spite of a two-week period of parenteral infection there was no break in the upward trend of the weight curve.

Chart 2 shows the composite curves of a group of sixty nine infants fed on soy bean milk only. There was no skimmed milk added and they received no breast milk. These curves are we believe, on a par

with the group mentioned above, who were given breast milk also. A larger number of the curves is above the Holt line, and the great majority closely parallel the line.

Chart 3 shows the curves of twenty-seven infants fed on breast milk plus the soy bean-skimmed milk mixture. Chart 4 represents a group of twenty-five infants fed on the soy bean-skimmed milk preparation minus breast milk. The curves in both of these charts further demonstrate the adequacy of the food.

Charts 7 and 8 illustrate the progress in two infants fed on the soy bean-skimmed milk mixtures. Baby N D (No 031217) received a

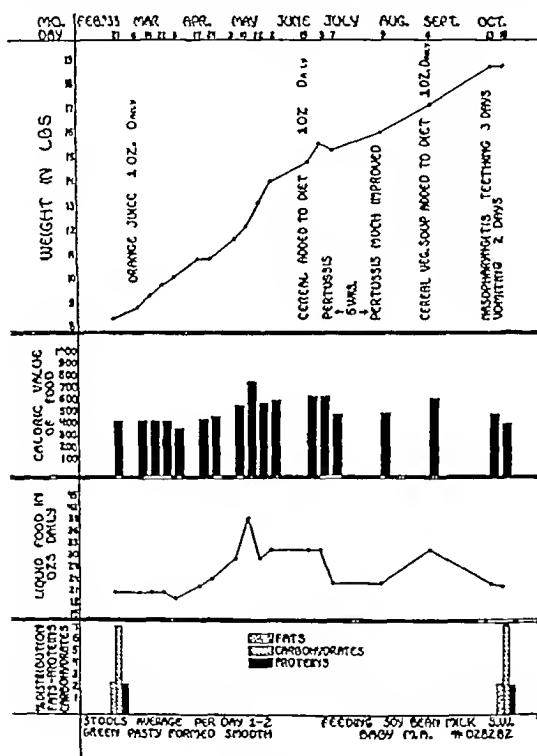


Chart 7

higher percentage of skimmed milk protein than did Baby M A (No 028282), yet there is little difference in their respective curves.

Growth and resistance to infections were good in practically all of the babies. The tissue turgor was excellent, their color was good, and their general development paralleled that of breast-fed infants and those fed on cow's milk preparations.

EFFECTS OF SOY BEAN MILK ON CONSTIPATION OF INFANTS

In our preliminary report we mentioned that a characteristic feature of the stools was the large bulk. This we attributed to the cellulose

3 Soy bean milk in combination with various percentages of skimmed milk protein affords a food of high nutritional availability

4 Blood studies have shown a normal range of calcium and phosphorus (serum), and roentgenologic studies demonstrate good bone development and texture with few exceptions. Suspicious signs of rickets in a few instances have not been corroborated clinically nor serologically.

5 The stool flora show a high percentage of gram-positive organisms, thus resembling those of breast-fed infants.

6 Soy bean milk is of practical value in the dietetic treatment of infantile eczema and in the treatment of constipation in infants by virtue of the "roughage" factor.

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10515 CARNEGIE AVENUE

7016 EUCLID AVENUE

1945 EAST NINETY SEVENTH STREET

RANGE AND STANDARD DEVIATIONS OF CERTAIN PHYSICAL MEASUREMENTS IN HEALTHY CHILDREN

WILLIAM PALMER LUCAS, M.D. AND HELEN BRENTON PRYOR, M.D.
SAN FRANCISCO, CALIFORNIA

ACCURATE anthropometric standards are necessary for the study of growth changes, development nutrition, and ductless glands. This requires quantitative measurements and statistical treatment of data.

For the most part, measurements of a large number of children have included only heights and weights.¹⁻³ Transverse body diameters determine body build and are gradually assuming much importance in the study of children.⁴⁻⁶ Body build is here used in the strict sense of type of bony framework designating large-boned and small boned individuals. State of nutrition has nothing to do with this definition of body build.

The necessity of an accurate objective method of measuring body build is emphasized by the demonstration of definite relationships of body build to nutrition,⁷⁻⁹ to oxygen consumption,⁷ and to physiology of the gastrointestinal tract.⁶ There is a presumptive relationship between body build and mental and personality make-up.^{10-12, 14, 15, 16} Finally there are certain suggestive findings in the field of immunology which associate disease susceptibility with general massiveness or lack of it.^{14, 16, 17}

Physical constitution is beginning to be recognized in America as a valuable approach in the appraisal of the child.¹⁸ Galton¹⁹ was a pioneer in the field of anthropometry and in the application of exact numerical values substituted for vague clinical estimates. He advocated recording measurements of body proportions strength, keenness of sense, energy, intellectual capacities, and mental character. Anthropometry may become the best key to whether development is normal or other wise. Endocrinologists consider divergence from certain physical standards as being due to endocrine dyscrasias.²⁰

The need for tables of normal measurements is obvious. The authors have been doing anthropometric measurements on San Francisco children for the past five years and have collected 5749 cases with ages ranging from six months to fifteen years.

Tables of constants presented are made up of measurements done on middle class, American born white children. They represent public school, private office practice and hospital clinic populations. All

children in the endocrine clinics and those suffering from any serious or chronic illness were excluded. We made sixty-three body measurements and worked out twenty-seven indices on the first one thousand children.

A number of these indices yielded substantially the same information and so were eliminated. Certain of the body measurements were found to contribute nothing toward classification of body build in the sense of designating large-boned and small-boned individuals, and consequently were not continued in the body build studies. Finally, thirteen measurements were chosen, and six indices were worked out from these as contributing differential items.

Technics of measuring were those described by Martin,²¹ Hrdlicka,²² and Draper²³ or those adopted by the International Anthropometric Agreement. Standard anthropometric instruments were used throughout. The large and small sliding calipers, spreading calipers, and anthropometric rod came from Zurich. Millimeter tapes with spring handles to regulate the tensions and subcutaneous tissue calipers came from the American Child Health Association, while a wooden sliding caliper graduated in both centimeters and inches came from the Marine Compass Company.

All measurements were done next to the skin, the children being stripped, except in the case of the public school examinations. In the schools the children removed their outer clothing and loosened the underclothing, permitting calipers to be slipped underneath.

Head diameters for breadth were measured euryon to euryon, for length, glabella to opisthocranium, with spreading calipers.*

Face and ear measurements were done with the small, straight-arm, sliding calipers. Face length was measured from menton to nasion, or tip of the chin to the suture between the nasal and frontal bones. Face breadth was measured as the distance between the two zygomatic processes.

Ear length was measured from superaurale to subaurale, and ear breadth, from preaurale to postaurale.

Interpupillary space was measured from the center of each pupil with eyes fixed.

*Anatomic landmarks follow Wilde's system of anthropometry.

1 Euryon—the two points opposite each other on the sides of the skull which form the termini of the line of greatest breadth.

2 Glabella—the most prominent point in the median line between the two eyebrow ridges a little above the frontonasal sutures.

3 Opisthocranium—the point is anatomically an indefinite one and is simply the posterior end of the maximum length line of the skull drawn from the glabella the point where the posterior leg of the compass rests when spanning the greatest length.

4 Superaurale—the highest point on the free margin of the ear.

5 Subaurale—the lowest point on the free margin (lobe) of the ear.

6 Preaurale—the most anterior point on the ear directly opposite the postaurale. The line between the preaurale and the postaurale is at right angles to the ear length line.

7 Postaurale—the most posterior point on the free margin of the ear.

The neck circumferences were measured just above the thyroid cartilage, the spring handle tape being used

Measurements of transverse chest were taken from the front with straight-arm calipers at the nipple level, the instrument being parallel to the floor. Readings were made during the middle phase of quiet respiration for chest diameters. Anterior and posterior chest diameters were made with the spreading curved arm calipers at the junction of the fourth rib with the sternum, the instrument parallel to the floor. This is the nipple level in boys and also in girls up to the age of complete development of the breasts, when the nipple level becomes variable.

Biacromial diameters were measured from the back while the hands were hanging straight to the sides. The sharp borders of the acromial processes were palpated from behind forward and measured firmly with the straight arm calipers held parallel to the floor.

The iliac diameter is considered the most important of the transverse diameters, since it is the best indicator of the width of the trunk. This measurement is not variable with posture or respiration and the landmarks are very definite. The iliac diameter was measured from the front with the straight arm calipers and using firm pressure to get as nearly as possible a skeletal or bony measurement of the widest flare of the iliac crest.

The indices calculated show up various body proportions and were calculated as follows

Cephalic head breadth divided by head length

Face facial height divided by bizygomatic diameter

Ear ear breadth divided by ear length

Neck neck length divided by neck circumference

Chest anteroposterior thoracic diameter divided by transverse thoracic diameter

Width length humeral diameter divided by standing height.

The width length index expresses width of the body in percentage of height or the relative width. This width length index has been found to be the best single measure of body build.

Our observations include 5,760 children from the ages of six months to sixteen years, which gives us between three and four hundred at each age level. These are about evenly divided between boys and girls. Statisticians agree that this is a large enough series to give adequate annual deviations.

The number of cases is indicated at the top of each table by age sex groups. The minimum and maximum, to show the smallest and largest observation made, indicate the range. The mean is the arithmetic mean and gives the average for the group of that particular measurement.

	Girls Age Under 1				Girls Age 1				Girls Age 2				Girls Age 3			
	NUMBER OF CASES 106				NUMBER OF CASES 163				NUMBER OF CASES 150				NUMBER OF CASES 148			
Cephalic Measurements	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	11 0-13 0	12 0	0 72		11 5-13 0	12 3	0 47		12 0-14 0	12 9	0 68		12 0-10 0	13 6	0 98	
Breadth	13 0-10 0	14 9	0 96		15 0-17 0	15 9	0 76		15 0-17 8	16 4	0 73		16 0-18 0	16 8	0 69	
Length	700 0-850 0	806 0	40 00		750 0-850 0	791 0	0 04		050 0-900 0	785 0	52 00		700 0-900 0	812 0	50 00	
Index																
Facial Measurements	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	5 0-7 5	6 5	0 49		5 0-8 5	7 1	0 59		7 0-9 7	7 8	0 51		7 0-9 0	8 1	0 72	
Height	9 0-11 5	10 1	0 83		9 0-11 5	10 3	0 42		9 0-11 2	10 4	0 63		9 5-11 2	10 0	0 57	
Zygomatic diameter	521 0-1064 0	709 8	77 00		454 0-762 0	646 3	80 00		030 0-842 0	748 0	68 00		625 0-850 0	761 0	67 00	
Index																
Ear Measurements	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	2 2-4 0	3 0	2 5		2 2-3 2	2 7	0 29		2 5-3 5	2 8	0 30		2 5-3 4	2 9	0 32	
Breadth	4 0-5 4	4 0	0 15		4 2-5 2	4 7	0 42		4 2-5 5	4 9	0 43		4 5-5 7	4 9	0 30	
Length	407 0-607 0	544 3	59 40		532 0-750 0	597 2	70 20		519 0-714 0	592 5	59 70		500 0-680 0	584 3	00 90	
Index																
Interpupillary Space	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	4 0-5 0	4 4	0 30		4 0-5 5	4 5	0 43		4 0-5 5	4 5	0 44		4 0-5 5	4 6	0 41	
Neck Measurements	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	3 5-9 0	6 1	1 80		5 0-10 0	7 7	1 60		7 0-14 0	8 9	2 10		7 0-13 0	9 0	1 30	
Length	19 0-28 0	22 5	2 80		20 0-25 0	22 7	1 40		21 0-20 0	23 0	1 00		22 0-26 0	23 8	1 60	
Circumference	159 0-391 0	270 7	68 70		217 0-500 0	340 6	78 00		304 0-538 0	387 1	63 90		260 0-545 0	411 6	09 00	
Index																
Trunk Measurements	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	10 2-13 0	11 4	0 99		11 0-13 0	12 2	0 99		11 5-14 0	12 6	0 88		11 5-15 0	13 1	1 31	
Ant post thor diam	11 0-16 0	13 3	0 85		13 0-16 0	14 7	1 15		13 0-17 0	15 6	1 32		14 0-18 0	16 1	0 97	
Lat thor diam	037 0-104 0	841 4	0 85		688 0-929 0	830 7	735 0-1000 0		735 0-1000 0	811 5	705 0-914 0		705 0-914 0	812 1	49 00	
Thor index	10 0-14 0	11 6	1 07		11 0-14 5	13 3	1 02		13 0-16 2	14 4	1 18		14 0-17 5	15 9	1 33	
Bihue diam	10 0-20 0	17 8	1 07		18 0-22 0	19 9	1 02		19 0-27 0	22 4	2 21		21 0-27 0	23 0	1 76	
Biacrom diam																
Width Length Index	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	150-190	175	7 95		150-192	172	0 97		152-194	171	7 33		147-188	168	7 30	

	Girls Age 4 NUMBER OF CASES 163				Girls Age 5 NUMBER OF CASES 184				Girls Age 6 NUMBER OF CASES 170				Girls Age 7 NUMBER OF CASES 102			
	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
<i>Cephalic Measurements</i>																
Breadth	12.0-15.0	13.0	0.86		13.0-15.0	13.7	0.69		13.0-14.5	13.7	0.40		13.0-14.5	13.9	0.51	
Length	16.0-18.0	17.2	0.62		16.0-18.5	17.3	0.50		16.0-18.0	17.3	0.71		16.0-18.0	17.7	0.80	
Index	100.0-830.0	786.0	50.00		700.0-830.0	703.0	30.00		700.0-870.0	789.0	38.00		700.0-850.0	784.0	37.00	
<i>Facial Measurements</i>																
Height	8.2-10.0	8.9	0.56		7.0-10.0	9.0	0.60		8.5-10.0	9.3	0.40		8.5-10.2	9.4	0.50	
Zygomatic diameter	10.0-13.0	10.8	0.79		10.0-12.0	11.1	0.53		10.0-12.0	11.0	0.50		8.0-12.0	11.2	0.70	
Index	760.0-950.0	830.3	49.30		636.0-905.0	795.0	68.70		772.0-920.0	905.2	57.90		756.0-1125.0	840.1	79.10	
<i>Ear Measurements</i>																
Breadth	2.2-3.3	2.8	0.35		2.2-3.5	2.8	0.53		2.5-3.4	2.8	0.26		2.5-3.4	2.8	0.20	
Length	4.5-5.0	5.0	0.30		4.5-7.0	5.2	0.58		4.7-6.4	5.4	0.35		3.5-6.2	5.4	0.59	
Index	429.0-600.0	535.5	60.00		430.0-737.0	546.2	21.30		386.0-640.0	530.8	60.00		402.0-830.0	540.7	60.40	
<i>Interapillary Space</i>																
	4.0-5.4	4.7	0.51		4.0-6.5	4.9	0.43		4.5-5.5	5.1	0.27		4.5-5.7	5.2	0.32	
<i>Nose Measurements</i>																
Length	7.0-12.0	9.2	1.20		8.0-13.0	9.9	1.50		8.0-14.0	10.7	1.90		9.0-10.0	11.0	1.40	
Circumference	92.0-200.0	24.0	2.10		23.0-29.0	24.0	1.60		20.0-20.0	25.6	1.80		22.4-20.0	27.2	1.80	
Index	274.0-500.0	374.8	70.90		308.0-432.0	401.2	62.80		333.0-542.0	419.7	98.30		340.0-660.0	452.0	98.90	
<i>Trunk Measurements</i>																
Ant. post. thor. diam.	12.0-15.0	13.4	1.17		12.0-15.0	13.6	1.41		11.5-17.0	14.2	1.30		13.0-15.0	14.7	1.40	
Lat. thor. diam.	15.0-20.0	17.2	1.61		15.0-19.2	17.4	1.33		16.0-20.0	17.0	1.42		16.7-21.0	18.3	1.38	
Thor. index	684.0-900.0	780.0	48.10		686.0-890.0	782.0	48.60		664.0-909.0	783.2	47.20		975.0-914.0	765.1	48.20	
Bilac. diam.	15.5-20.0	17.3	1.34		15.0-20.0	17.6	1.36		16.0-21.0	18.3	1.38		17.0-22.0	19.0	1.54	
Biacrom. diam.	22.0-30.0	25.0	2.57		22.0-30.0	26.8	2.20		24.0-33.0	28.0	2.21		26.0-35.0	29.6	2.04	
<i>Width Length Index</i>																
	1.44-184	164	7.84		1.44-184	161	7.84		1.40-180	159	8.42		1.44-174	150	7.63	

	Girls Age 8				Girls Age 9				Girls Age 10				Girls Age 11			
	NUMBER OF CASES 173				NUMBER OF CASES 158				NUMBER OF CASES 232				NUMBER OF CASES 194			
	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
<i>Cephalic Measurements</i>																
Breadth	13 0-15 0	14 1	0 56		13 0-15 0	14 1	0 49		13 4-15 0	14 2	0 49		13 0-15 5	14 3	0 62	
Length	16 0-19 0	17 8	0 71		16 2-19 0	17 8	0 63		17 0-19 0	17 9	0 63		17 0-19 0	17 9	0 55	
Index	722 0-875 0	791 8	43 40		722 0-853 0	788 6	29 90		724 0-833 0	790 7	26 40		722 0-912 0	803 0	39 90	
<i>Facial Measurements</i>																
Height	8 5-10 7	9 8	0 52		9 0-10 5	9 8	0 36		9 0-11 0	10 2	0 62		9 8-11 6	10 4	0 49	
Zygomatic diameter	9 5-12 5	11 5	0 78		10 0-12 5	11 5	0 65		10 0-13 0	11 8	0 63		10 0-13 0	11 9	0 76	
Index	708 0-1054 0	862 9	79 30		792 0-945 0	857 6	48 80		750 0-1110 0	868 9	66 70		800 0-1050 0	874 8	71 50	
<i>Ear Measurements</i>																
Breadth	2 4-3 5	2 8	0 26		2 3-3 5	2 9	0 44		2 4-3 4	2 9	0 31		2 4-3 5	2 9	0 31	
Length	4 7-6 5	5 6	0 44		4 7-6 3	5 6	0 49		5 0-6 4	5 7	0 42		5 2-6 5	5 7	0 42	
Index	400 0-600 0	499 0	45 60		444 0-648 0	553 8	54 30		421 0-640 0	521 4	48 00		387 0-577 0	499 7	53 90	
<i>Interpapillary Space</i>																
	4 0-5 7	5 2	0 41		4 8-5 7	5 2	0 29		4 6-6 0	5 4	0 35		4 7-6 4	5 6	0 36	
<i>Neck Measurements</i>																
Length	7 0-15 0	11 2	2 00		7 0-15 0	11 2	2 20		5 0-17 0	11 3	2 30		8 0-17 0	11 5	2 10	
Circumference	23 0-30 0	27 3	2 10		25 0-31 0	27 5	1 50		26 0-31 0	28 3	1 30		27 0-33 5	29 0	1 40	
Index	241 0-549 0	416 4	82 90		241 0-536 0	392 6	79 90		185 0-629 0	393 3	90 40		258 0-531 0	390 1	75 70	
<i>Trunk Measurements</i>																
Ant post. thor diam	12 5-17 5	14 8	1 24		13 0-18 0	14 9	1 31		13 0-18 5	15 3	1 51		13 5-20 0	16 4	1 75	
Lat thor diam.	17 0-22 0	19 1	1 19		18 2-23 0	19 9	1 89		19 0-24 0	20 8	1 62		18 0-27 2	22 0	2 03	
Thor index	650 0-944 0	776 2	55 12		650 0-900 0	754 0	60 20		619 0-842 0	747 9	52 20		537 0-889 0	738 2	58 00	
Bilac diam	18 0-22 0	20 3	1 56		18 5-23 0	21 1	1 97		20 0-26 5	22 1	1 72		20 0-29 5	23 1	1 84	
Bucron diam.	22 0-34 0	30 8	2 38		26 0-34 0	31 1	2 31		28 0-38 0	32 2	2 11		29 0-38 0	33 0	2 58	
<i>Width Length Index</i>																
	140 - 174	159	7 49		142 -174	159	6 11		134 - 185	160	9 85		140 - 185	161	8 90	

	Girls Age 12			Girls Age 13			Girls Age 14			Girls Age 15		
	NUMBER OF CASES 258			NUMBER OF CASES 265			NUMBER OF CASES 183			NUMBER OF CASES 151		
	RANGE	MEAN	SIGMA	RANGE	MEAN	SIGMA	RANGE	MEAN	SIGMA	RANGE	MEAN	SIGMA
Cephalic Measurements												
Breadth	13.0-15.5	14.4	0.64	13.0-16.0	14.4	0.40	14.0-15.0	14.5	0.33	14.0-15.5	14.6	0.52
Length	16.2-20.0	18.4	0.83	17.0-20.0	18.4	0.72	17.0-20.0	18.5	0.73	18.0-20.0	18.5	0.60
Index	70.0-87.0	77.3	44.70	71.0-89.0	77.5	44.00	78.7-84.0	781.5	35.90	71.0-88.0	776.3	47.00
Facial Measurements												
Height	10.0-11.0	10.5	0.43	9.8-11.7	10.7	0.47	10.5-11.5	10.8	0.52	10.0-11.8	11.0	0.54
Zygomatic diameter	11.0-13.0	11.9	0.76	10.5-14.0	12.1	0.94	12.0-14.0	13.8	0.75	12.0-14.0	12.8	0.44
Index	80.0-100.0	89.2	74.70	82.0-97.0	88.4	55.20	80.0-95.0	850.2	30.60	83.0-94.0	884.9	34.60
Ear Measurements												
Breadth	3.4-3.5	3.0	0.29	3.4-3.4	3.9	0.35	3.4-3.5	3.0	0.25	3.3-3.5	3.0	0.27
Length	5.0-6.4	5.5	0.35	5.2-6.2	5.8	0.34	5.0-6.5	6.0	0.15	5.4-6.9	6.0	0.30
Index	45.0-64.0	53.1	65.50	40.0-69.0	51.6	62.20	45.0-63.0	400.5	38.60	40.0-50.0	504.4	40.00
Interpapillary Space												
	4.8-6.5	5.7	0.43	4.7-6.4	5.7	0.45	4.6-6.4	5.9	0.30	4.3-6.4	5.9	0.44
Neck Measurements												
Length	8.0-20.0	12.6	3.30	9.0-17.0	12.8	2.90	9.0-20.0	14.3	3.50	9.0-17.0	14.2	2.40
Circumference	27.0-35.0	29.1	1.60	28.0-33.0	30.5	0.80	29.0-33.0	31.2	1.10	30.0-34.0	32.1	1.20
Index	200.0-645.0	432.4	114.10	300.0-400.0	370.1	40.00	290.0-415.0	465.5	115.9	285.0-530.0	443.7	86.10
Trunk Measurements												
Ant. post. thor diam.	13.2-22.0	16.7	1.81	14.0-20.5	16.7	1.71	15.0-23.0	17.8	1.81	14.2-23.0	17.9	2.13
Lat. thor diam.	20.0-26.5	23.1	1.76	20.5-29.0	24.1	2.04	19.0-28.0	24.9	1.75	22.0-28.0	24.9	1.93
Thor index	60.0-95.0	74.5	50.00	63.0-77.0	69.1	48.10	77.0-86.0	704.3	49.90	60.0-86.0	730.4	41.10
Pelvic diam.	30.0-32.0	31.1	2.35	19.0-20.0	25.1	2.13	20.0-29.5	25.8	2.13	21.0-31.5	26.2	2.39
Biacrom. diam.	30.0-40.0	35.5	2.00	29.0-39.0	35.9	2.19	28.0-43.0	35.9	2.43	33.0-40.0	36.2	1.99
Width Length Index												
	139-184	162	9.21	143-180	163	10.46	139-185	163	11.07	141-184	164	9.65

	Boys Age Under 1				Boys Age 1				Boys Age 2				Boys Age 3			
	NUMBER OF CASES 109				NUMBER OF CASES 170				NUMBER OF CASES 154				NUMBER OF CASES 162			
<i>Cephalic Measurements</i>	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	120-140	127	0.04		120-140	132	0.71		120-150	136	1.04		130-145	138	0.50	
Length	140-160	153	0.56		150-180	164	0.97		100-190	170	0.95		100-180	173	0.66	
Index	7000-9000	8260	70.00		7000-9000	8060	64.00		6500-8500	7980	59.00		7000-8500	7800	52.00	
<i>Facial Measurements</i>	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	50-80	07	0.57		70-85	74	0.45		70-95	81	0.55		70-95	84	0.61	
Height	90-120	102	0.74		90-120	104	0.82		100-115	106	0.42		100-120	108	0.64	
Zygomatic diameter	5830-8890	0982	82.90		5400-8000	6776	81.80		6600-8030	7387	80.90		6360-10890	7923	79.00	
<i>Ear Measurements</i>	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	21-35	20	0.10		25-33	28	0.28		25-34	29	0.34		25-34	29	0.29	
Length	42-55	47	0.12		42-55	49	0.38		50-55	52	0.17		45-60	52	0.48	
Index	4200-6430	5501	59.40		4750-7140	5824	60.60		4540-6860	5090	24.00		5000-6060	5728	57.60	
<i>Interpapillary Space</i>	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	40-52	46	0.27		42-52	47	0.38		45-55	47	0.34		37-60	48	0.67	
<i>Neck Measurements</i>	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	50-100	08	1.62		50-145	87	2.40		70-110	87	1.20		55-120	88	2.10	
Length	200-270	228	1.82		210-270	237	2.30		215-200	240	1.00		220-290	250	2.00	
Circumference	1850-4140	3027	73.00		2080-5370	3695	90.10		2740-4780	3850	69.30		2200-5000	3520	72.10	
<i>Trunk Measurements</i>	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	100-120	112	0.03		102-140	123	0.90		112-145	125	1.46		120-150	136	1.08	
Ant post thor diam	120-150	130	0.95		140-172	152	1.58		150-180	161	1.47		150-190	166	1.37	
Lat thor diam	6320-9300	8046	0390		9330	8135	7000		9000	8041	6090		9060	8072	1.33	
Thor index	110-142	122	1.00		110-140	131	1.10		130-160	145	1.56		140-180	160	1.91	
Bulnar diam	160-270	187			180-230	205	1.50		200-230	219	2.64		220-300	240	1.91	
Bacrom diam																
<i>Width Length Index</i>	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
	155-190	173	7.33		150-190	168	0.54		146-184	167	6.98		145-190	166	7.20	

	Boys Age 4			Boys Age 5			Boys Age 6			Boys Age 7		
	NUMBER OF CASES 133			NUMBER OF CASES 101			NUMBER OF CASES 176			NUMBER OF CASES 163		
<i>Cephalic Measurements</i>												
Breadth	RANGE 13.0-15.0	MEAN 14.1	SIGMA 0.64	RANGE 12.5-15.0	MEAN 14.1	SIGMA 0.84	RANGE 13.0-16.0	MEAN 14.2	SIGMA 0.61	RANGE 13.0-15.0	MEAN 14.2	SIGMA 0.70
Length	RANGE 16.0-20.0	MEAN 17.9	SIGMA 0.83	RANGE 16.0-20.0	MEAN 18.0	SIGMA 1.09	RANGE 17.0-19.0	MEAN 18.1	SIGMA 0.83	RANGE 16.0-20.0	MEAN 18.1	SIGMA 1.02
Index	RANGE 70.0-80.0	MEAN 79.0	SIGMA 37.00	RANGE 65.0-80.0	MEAN 77.0	SIGMA 39.00	RANGE 70.0-85.0	MEAN 78.7	SIGMA 44.00	RANGE 70.0-90.0	MEAN 79.4	SIGMA 52.00
<i>Facial Measurements</i>												
Height	RANGE 7.0-10.5	MEAN 8.9	SIGMA 0.50	RANGE 8.5-10.7	MEAN 9.1	SIGMA 0.34	RANGE 9.0-11.0	MEAN 9.8	SIGMA 0.44	RANGE 8.5-10	MEAN 9.0	SIGMA 0.47
Zygomatic diameter	RANGE 10.7-12.0	MEAN 11.1	SIGMA 0.71	RANGE 10.0-12.0	MEAN 11.1	SIGMA 0.57	RANGE 10.0-12.0	MEAN 11.4	SIGMA 0.68	RANGE 11.0-12.0	MEAN 11.4	SIGMA 0.38
Index	RANGE 127.0-140.0	MEAN 139.1	SIGMA 71.50	RANGE 108.0-120.0	MEAN 113.0	SIGMA 65.40	RANGE 102.0-135.0	MEAN 114.0	SIGMA 40.30	RANGE 118.0-145.0	MEAN 130.0	SIGMA 57.60
<i>Ear Measurements</i>												
Breadth	RANGE 2.7-3.2	MEAN 2.9	SIGMA 0.24	RANGE 2.5-3.1	MEAN 2.8	SIGMA 0.23	RANGE 2.7-3.8	MEAN 3.1	SIGMA 0.31	RANGE 2.7-3.0	MEAN 3.1	SIGMA 0.27
Length	RANGE 5.0-6.0	MEAN 5.4	SIGMA 0.28	RANGE 4.3-5.5	MEAN 5.4	SIGMA 0.37	RANGE 4.0-6.4	MEAN 5.0	SIGMA 0.53	RANGE 4.5-6.2	MEAN 5.7	SIGMA 0.45
Index	RANGE 47.0-60.0	MEAN 54.6	SIGMA 48.50	RANGE 50.0-70.0	MEAN 58.2	SIGMA 39.30	RANGE 46.0-68.0	MEAN 56.3	SIGMA 36.50	RANGE 43.0-60.0	MEAN 54.2	SIGMA 47.30
<i>Interpupillary Space</i>												
	RANGE 3.7-4.0	MEAN 3.9	SIGMA 0.48	RANGE 4.5-6.0	MEAN 5.1	SIGMA 0.50	RANGE 4.4-6.0	MEAN 5.1	SIGMA 0.41	RANGE 4.5-5.7	MEAN 5.2	SIGMA 0.37
<i>Accl. Measurements</i>												
Length	RANGE 0.0-13.0	MEAN 8.9	SIGMA 2.10	RANGE 0.0-14.0	MEAN 10.1	SIGMA 2.20	RANGE 7.0-14.0	MEAN 10.3	SIGMA 1.00	RANGE 3.0-14.0	MEAN 11.4	SIGMA 1.50
Circumference	RANGE 24.0-29.0	MEAN 26.0	SIGMA 0.90	RANGE 24.0-27.5	MEAN 26.5	SIGMA 1.70	RANGE 24.5-29.0	MEAN 26.0	SIGMA 1.30	RANGE 2.0-29.0	MEAN 26.7	SIGMA 1.40
Index	RANGE 73.0-131.0	MEAN 93.7	SIGMA 71.00	RANGE 74.0-141.0	MEAN 99.9	SIGMA 70.00	RANGE 70.0-150.0	MEAN 99.4	SIGMA 59.00	RANGE 70.0-157.0	MEAN 100.8	SIGMA 66.70
<i>Thumb Measurements</i>												
Ant. post. thor. diam.	RANGE 12.0-15.0	MEAN 14.0	SIGMA 1.22	RANGE 13.0-15.5	MEAN 14.5	SIGMA 1.20	RANGE 13.2-16.0	MEAN 14.7	SIGMA 1.15	RANGE 13.0-16.0	MEAN 14.9	SIGMA 1.31
Lat. thor. diam.	RANGE 15.2-20.0	MEAN 17.6	SIGMA 1.10	RANGE 15.0-22.0	MEAN 17.8	SIGMA 1.44	RANGE 17.0-21.0	MEAN 18.8	SIGMA 1.01	RANGE 17.0-21.0	MEAN 19.8	SIGMA 1.84
Thor. index	RANGE 60.0-82.0	MEAN 79.0	SIGMA 0.90	RANGE 63.0-83.0	MEAN 80.0	SIGMA 0.90	RANGE 60.0-83.0	MEAN 78.6	SIGMA 0.90	RANGE 60.0-83.0	MEAN 78.5	SIGMA 0.540
Biacrom. diam.	RANGE 15.0-19.5	MEAN 17.2	SIGMA 1.20	RANGE 16.5-20.0	MEAN 18.1	SIGMA 1.28	RANGE 16.2-22.0	MEAN 18.5	SIGMA 1.07	RANGE 17.0-21.2	MEAN 19.3	SIGMA 1.55
Biacrom. diam.	RANGE 20.0-32.0	MEAN 25.0	SIGMA 2.39	RANGE 23.0-30.0	MEAN 26.2	SIGMA 1.77	RANGE 26.0-32.0	MEAN 29.0	SIGMA 2.48	RANGE 25.0-36.0	MEAN 30.0	SIGMA 2.43
<i>Width Length Index</i>												
	RANGE 139-180	MEAN 162	SIGMA 7.70	RANGE 139-190	MEAN 161	SIGMA 7.27	RANGE 139-180	MEAN 160	SIGMA 6.76	RANGE 140-174	MEAN 159	SIGMA 6.48

	Boys Age 8				Boys Age 9				Boys Age 10				Boys Age 11			
	NUMBER OF CASES 166				NUMBER OF CASES 167				NUMBER OF CASES 218				NUMBER OF CASES 193			
	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
<i>Cephalic Measurements</i>																
Breadth	130-150	143	0.38		135-150	144	0.51		130-150	146	0.41		134-160	146	0.73	
Length	170-192	182	0.52		170-190	182	0.63		172-200	183	0.62		170-195	185	0.74	
Index	733 0-834 0	787.8	24.70		765 0-880 0	793.1	33.90		700 0-943 0	796.6	36.30		705 0-889 0	783.9	50.00	
<i>Facial Measurements</i>																
Height	92-110	101	0.59		95-110	101	0.48		97-117	105	0.59		97-116	105	0.50	
Zygomatic diameter	110-124	117	0.55		110-125	118	0.76		110-130	122	0.71		110-140	124	0.59	
Index	767 0-945 0	866.7	60.10		832 0-1000 0	882.7	75.00		808 0-955 0	857.1	59.10		770 0-917 0	812.8	61.50	
<i>Ear Measurements</i>																
Breadth	30-34	31	0.20		28-35	31	0.17		27-34	31	0.20		28-45	31	0.51	
Length	50-67	59	0.45		50-62	59	0.38		55-67	59	0.33		50-70	59	0.32	
Index	477 0-600 0	522.8	36.40		500 0-600 0	542.0	33.70		448 0-545 0	505.1	26.20		429 0-750 0	540.1	96.00	
<i>Interpapillary Space</i>																
	45-62	53	0.51		45-62	55	0.36		47-62	55	0.47		47-62	55	0.46	
<i>Neck Measurements</i>																
Length	80-140	112	2.20		90-130	110	0.30		80-140	119	2.30		80-160	122	3.00	
Circumference	240-330	276	2.10		250-320	285	2.20		270-350	298	2.30		280-330	299	1.40	
Index	233 0-500 0	362.9	84.30		312 0-500 0	401.2	54.20		281 0-481 0	366.6	65.30		256 0-571 0	409.0	99.80	
<i>Trunk Measurements</i>																
Ant. post thor diam	140-180	157	1.28		130-170	158	1.19		145-190	167	1.55		150-195	167	1.52	
Lat thor diam	180-280	201	2.20		180-230	206	1.83		180-255	217	1.57		180-250	219	1.55	
Thor index	700 0-895 0	780.7	50.90		650 0-944 0	755.9	51.80		640 0-867 0	775.2	51.00		660 0-944 0	784.3	58.70	
Biacrom diam	180-225	203	2.02		190-250	211	2.30		190-248	216	1.63		205-260	223	1.75	
Biacrom diam	290-370	319	2.71		280-360	325	2.64		300-410	344	2.40		300-400	348	2.52	
<i>Width Length Index</i>																
	140-178	158	7.32		140-180	157	6.49		134-180	158	7.80		139-184	157	7.59	

	Boys Age 12				Boys Age 13				Boys Age 14				Boys Age 15			
	NUMBER OF CASES		260		NUMBER OF CASES		264		NUMBER OF CASES		106		NUMBER OF CASES		119	
	RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA		RANGE	MEAN	SIGMA	
<i>Cephalic Measurements</i>																
Breadth	13.0-16.5	14.7	0.56		13.5-16.0	14.7	0.77		18.4-16.2	14.8	0.52		13.0-16.0	15.0	1.41	
Length	17.0-20.0	18.5	0.78		17.0-20.0	18.5	0.78		17.0-20.0	18.6	0.54		17.0-20.0	18.7	0.45	
Index	725.0-872.0	781.7	37.90		737.0-841.0	797.3	81.40		692.0-790.0	739.7	32.20		780.0-823.0	800.5	45.70	
<i>Facial Measurements</i>																
Height	10.0-12.0	10.5	0.50		10.0-12.0	10.8	0.50		10.4-12.0	11.3	0.59		10.5-12.0	11.3	0.68	
Zygomatic diameter	11.0-13.5	12.8	0.81		11.0-15.0	12.8	0.79		13.0-14.0	13.0	0.71		12.0-14.0	13.0	0.63	
Index	832.0-1000.0	906.5	74.70		733.0-955.0	859.5	50.80		857.0-960.0	908.8	33.40		808.0-876.0	860.5	20.80	
<i>Ear Measurements</i>																
Breadth	2.5-4.0	3.1	0.53		3.0-3.5	3.2	0.23		3.0-3.4	3.3	0.23		2.7-3.5	3.3	0.33	
Length	5.2-6.5	5.9	0.48		5.4-7.0	6.0	0.40		8.0-7.4	8.8	0.50		6.2-7.0	6.8	0.20	
Index	308.0-515.0	489.5	96.00		476.0-618.0	531.0	36.50		422.0-548.0	483.3	40.10		436.0-531.0	470.2	48.00	
<i>Interpapillary Space</i>																
	4.5-6.0	5.3	0.41		5.2-6.4	5.5	0.35		5.2-6.0	5.6	0.38		5.2-6.5	5.9	0.52	
<i>Veet Measurements</i>																
Length	0.0-16.3	12.3	2.90		7.0-17.0	12.5	2.40		10.0-10.5	13.3	2.50		10.0-15.0	12.8	2.50	
Circumference	27.5-31.0	30.3	3.30		25.0-38.0	30.5	2.50		32.0-36.0	33.1	2.40		30.0-39.0	35.0	3.00	
Index	303.0-600.0	409.0	82.80		269.0-531.0	410.3	74.40		312.0-500.0	405.7	81.80		279.0-486.0	373.5	63.20	
<i>Tranal Measurements</i>																
Ant. post. thor diam.	14.5-19.0	18.9	1.54		15.0-31.0	17.8	2.20		18.0-34.0	20.1	2.49		17.0-27.0	21.7	2.09	
Lat. thor diam.	19.0-23.0	21.0	1.68		20.0-26.5	23.4	2.41		22.0-29.0	25.4	2.43		22.0-30.0	26.8	2.28	
Thor index	65.0-905.0	753.0	57.20		500.0-909.0	755.7	56.40		714.0-845.0	793.0	55.40		800.0-808.0	781.7	60.80	
Biflacc diam.	31.0-25.0	23.1	1.52		31.0-3.0	23.6	1.89		21.5-28.5	24.9	2.14		24.0-31.5	25.4	2.43	
Biacrom diam.	3.0-37.5	35.9	2.54		33.0-42.0	30.9	1.74		35.0-40.0	38.3	2.62		35.0-43.5	38.5	2.55	
<i>Width Length Index</i>																
	140-175	157	7.21		144-180	156	7.84		139-180	155	7.25		135-184	155	8.08	

The sigma or standard deviation is the most important constant, since it shows the amount of variation around the average. The word "normal" has ceased to mean "average" and has taken on rather the meaning of falling into certain ranges or zones of variation from average. Porter²⁴ in 1893 recognized it when he said the average was "that value which is as often exceeded as attained."

Standard deviations help to mark off these zones of normality. The zone included between one standard deviation plus and one standard deviation minus the average, takes in 67 per cent of the general population, leaving 16.5 per cent to vary more than one standard deviation in either direction. This will be true of any series of biologic data which is large enough to give statistical constants.

For purposes of designating an arbitrary line in classifying children, we have used the standard deviation as a convenient unit of measure because of the mathematical and statistical logic of this unit.

Hejman and Hatt²⁵ stressed the importance of measuring the variation within, as well as the central tendency of, the age group in interpreting body measurements in young children.

Having fulfilled the statistical requirements for number of cases and homogeneity, we feel that comparing physical measurements of a given child of similar social status with this series should indicate something of his consistency of development. In other words, it should show up his disharmonies if he fell within one zone for chest development and another zone for lower trunk development.

The child whose physical traits all fell within the same zone, who varied from the average in the same direction and approximately the same amount for his different traits, would be classified as normal whether he were much smaller than average or much larger than average.

The importance of indices is seen when interpreting absolute measurements which vary markedly from the average in either direction. Interpretation depends upon relative size and not upon absolute size. Thus a child whose chest or pelvic measurements were very small may be found to be short in stature too, consequently making his body proportions normal. Conversely, if the transverse diameters are very large and the child is found to be taller than average, his body proportions may be very similar to the short child with narrow diameters. Indices compare the relative build of a child with others of his own age sex group or with those of different ages equally well.

Indices also show up the interrelationship of various body proportions to the others in the same child, i.e., a child may have a relatively small chest and a relatively large head.

Boas²⁶ found that

A Variability of annual growth increased with age

B Young children grow more uniformly than older ones

C Variability is greatest during adolescence

D Growth of girls is more variable than that of boys.

These four points are all confirmed and demonstrated in our tables

Boas concluded that during the early years of childhood short children grow more slowly than tall children. During adolescence they continue to grow, while tall children have more nearly reached their full development. Smallness may therefore be due to slowness of development.

Differences in development between various social classes are, to a great extent, results of acceleration and retardation of growth which act in such a way that the social groups which show higher values of measurement do so on account of accelerated growth, and they cease to grow earlier than those whose growth is in the beginning less rapid so that there is a tendency to decreasing differences between these groups during the last years of growth

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THE EFFECT OF PLACENTAL EXTRACT ON THE DICK TEST

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IN 1933 McKhann and Chu¹ reported the successful separation from the human placenta of an extract composed largely of pseudoglobulins which they showed to have several important immunologic properties. Among these was the ability to blanch scarlet fever rashes, in some instances more effectively than scarlet fever antitoxin. Despite the fact that there is considerable uncertainty about the immunologic aspects of scarlet fever and the relation of the Dick toxin to it, it seems fairly definitely established as the result of the work of the Dicks and others that most individuals exhibiting a positive Dick test are susceptible to scarlet fever and that the test may be regarded as a quantitative as well as a qualitative measure of the degree of susceptibility to the disease.

It was thought therefore that some light might be shed on the action of the placental extract if one were to administer it to a group of children who reacted positively to the Dick test and follow this administration by repeated Dick tests at frequent intervals, considering any variation in the size of the reaction as an indication of changed levels of immunity to scarlet fever. This would seem particularly interesting in the absence of any published work on the use of the extract in preventing scarlet fever in exposed susceptible subjects, similar to its use already reported in measles.

The study was undertaken on fifteen children being treated for orthopedic conditions in the Shriners' Hospital for Crippled Children, who were found to react positively to the Dick toxin as prepared by the Connaught Laboratories, Toronto. None of these patients had had scarlet fever. Their ages varied from fifteen months to fourteen and one-half years. The placental extract was administered intramuscularly in single doses of 5 c.c. or 10 c.c.

In most cases there were complaints of considerable discomfort at the site of injection for several hours. In no instance was there fever or other evidence of systemic reaction.

The precautions suggested by the Dicks² to assure accurate readings were observed. The tests were read in twenty-four hours and measured carefully by the author. In the event of oval reactions the mean of the length and breadth was considered as the diameter.

From the Henry J. Elliott Research Fund of the Shriners Hospital for Crippled Children, Montreal Unit.

The controls consisted of five children with positive Dick tests, chosen at random, to these no extract was given.

Chart 1 shows graphically the effect of the extract on the Dick tests of these children. Table I gives the dosages, ages, etc. It will be seen that the controls remained relatively unchanged by the repeated injections of toxin, at least over the period of observation. All the children who received extract showed a tendency to become almost or definitely Dick negative in a few days with a tendency to become Dick positive again in a varying period. Eight of the fifteen reached or fell below the

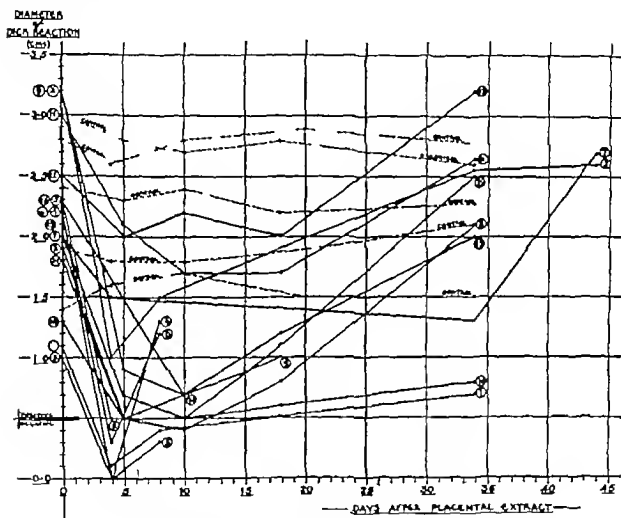


Chart 1.—Showing variations in the size of Dick tests made at intervals after administration of placental extract to fifteen Dick positive children.

level (0.5 cm.) generally considered the borderline between positive and negative Dick tests. The amount of material administered and the age of the patient bore no relation to the rapidity of fall in the curves the level to which they returned, or the rate of return.

Interpreting these findings in terms of immunity to scarlet fever, one may say that the placental extract* used in this study in a small series of children was able to produce, in the majority of cases rapid reduction

*The placental extract used in this study was kindly furnished by E. R. Squibb & Sons.

in the susceptibility to scarlet fever as indicated by the changing of a positive Dick test into a negative one

TABLE I

THE AGE AND SEX OF PATIENT AND LOT NUMBER AND DOSAGE OF
EXTRACT ADMINISTERED

PATIENT	AGE IN YR.	SEX	EXTRACT LOT NO	DOSE	HOSP NO
A S	29 $\frac{1}{12}$	M	51944	5 cc	1691
M C	69 $\frac{1}{12}$	F	51944	5 cc	1792
A D	13 $\frac{1}{12}$	M	51944	5 cc	1782
R B	35 $\frac{1}{12}$	M	51944	5 cc	1714
N A.	49 $\frac{1}{12}$	M	51944	5 cc	1399
F K	11	M	51944	5 cc	791
C M	89 $\frac{1}{12}$	M	51944	5 cc	1639
M M	114 $\frac{1}{12}$	M	51944	10 cc	1858
V G	9	M	51944	10 cc	1865
C J	24 $\frac{1}{12}$	M	52404	5 cc	1835
N S	13	F	52404	10 cc	1816
H K.	73 $\frac{1}{12}$	F	52404	10 cc	1709
M R	108 $\frac{1}{12}$	F	52404	10 cc	1722
N L	25 $\frac{1}{12}$	F	52404	5 cc	1841
B B	145 $\frac{1}{12}$	F	52404	10 cc	937

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DRUMMOND MEDICAL BUILDING

Pediatric Clinics

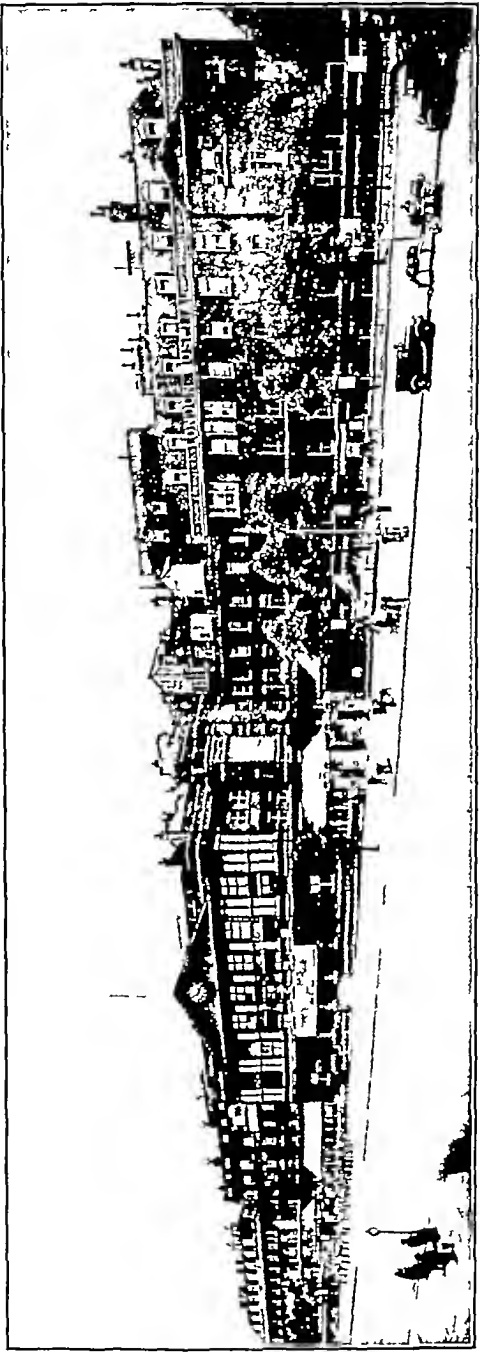
THE CHILDREN'S DEPARTMENT OF THE LONDON HOSPITAL ENGLAND

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THE London Hospital, which is the largest voluntary and teaching hospital in England, is situated in Whitechapel, in the east end of London one of the poorest and most crowded sections of the city. It has a total of 856 beds, and the out-patient attendances number approximately 10 000 per week. As may be imagined the wealth of clinical material is unrivalled, for apart from the mere question of numbers, the Hospital draws not only from the east end of the city but also from the whole of the Thames dock areas, and from the districts running down to the southeast coast of England.

When one considers the size of this hospital, it may appear surprising that the formation of a special children's department was a comparatively recent development. In this respect the London Hospital is not, however, backward among general hospitals in this country for the formation of children's departments in the English teaching hospitals is really a postwar development. Prior to 1918 such departments were most exceptional, and their formation in some hospitals has occurred only very recently. There are still large teaching hospitals in London without special children's departments although, of course children are treated in these hospitals. The reason for the comparatively recent inauguration of these special departments is to be found in the fact that the medical profession in England has viewed such specialisation with some misgiving owing to its inherent disadvantages. So far as paediatrics is concerned, it has been felt that the general physician is a proper and competent person to deal with the sick child that were he to relinquish this work his medical knowledge and experience would suffer as a result of his being divorced from the opportunity of seeing disease in some of its early phases peculiar to childhood that on the other hand the man who dealt purely with children would have his outlook limited and his experience curtailed—at any rate in regard to prognosis—by losing sight of his patients after they had attained a certain age. That this attitude is an understandable one nobody can deny. There are, however, manifest advantages in having a purely paediatric department and the patient in particular would seem on the whole to reap the benefit of being under the care of a physician specially trained and experienced in paediatrics. One may state that this principle is now as firmly established here as abroad. This is shown by the fact that special children's departments have come into being in most of the large general teaching hospitals. In these there is the special advantage that the paediatrician owing to contact with his colleagues and to the proximity of adult patients, is certainly less likely to lose touch with general medicine than might be the case if he were working exclusively in a children's hospital.

It was at the commencement of 1921 that the first move was made toward the formation of a special children's department in the London Hospital. Till then, children had been treated as out-patients and in-patients by the general physicians to the hospital without special segregation although two children's medical wards,



The London Hospital

with a total of forty two beds had been set apart for patients up to the age of seven years. (This age limit has recently been raised to twelve years.) At the date above mentioned, the Medical Council recommended that in the interests of all concerned a special treatment centre for the care of infants and children under five years of age should be instituted within the Hospital. The Hospital Committee agreed with this recommendation, and consequently a special out patient session for young children was inaugurated. Dr Charles Miller a physician already on the hospital staff, was selected as being peculiarly suited for taking charge of the new venture. It was not, however until a few years later that a true children's department was instituted. In 1925 Dr A. G. Maitland Jones, who had previously assisted Dr Miller, was appointed to the honorary staff of the hospital as physician in charge of the children's department, and this department designed to deal with children from infancy to school leaving age, commenced its work in July 1926. Like its fellows in other English hospitals, the department constituted a unit for dealing with the care management, and medical diseases of infants and children. Children suffering from surgical conditions, on the other hand were dealt with as previously along with the general surgical patients, although for inpatients there were as heretofore two children's surgical wards.

The children's department commenced its work with out patients in accommodation which although possible, was by no means ideal. At first two morning sessions a week were devoted to the work but very soon a third was added, in which only old patients were seen. Shortly after the opening of the out patient clinic, one of the children's wards of twenty one beds was completely taken over by the department, and a little later five beds in adult wards, available for children up to sixteen years of age, were allotted to it. The importance of this latter arrangement lies in the necessity for being able to admit to hospital any children attending the out patient clinic, without being confined to the age limit required for admission to the children's ward. It may be asked why only one of the two children's medical wards was taken over in forming a special department. The reason for this is that hitherto the beds in both wards had been shared by the general physicians to the hospital, and in order to avoid severing their connection with children entirely, it was decided that only one ward should be allotted to the newly formed children's department and that the beds in the other ward should be shared as before among the general physicians, who could thus, to the advantage of themselves and of their house physicians (resident medical officers) keep in touch with medical conditions peculiar to childhood. The beds in this ward are kept filled by cases demanding urgent admission to the hospital on certain days of the week, while the children's department ward draws its patients from its own out patient department (to which all children requiring out patient treatment are referred) and from emergency admissions on the remaining days of the week.

In addition to the physician in-charge, the staff of the department consisted at the outset of a first assistant, a resident house physician, and two clinical assistants. The work grew with great rapidity and expansions in various directions were required. In 1930 an entirely new set of rooms was erected to our requirements and design, the whole layout of waiting rooms, dressing and weighing rooms and rooms for consultation and treatment being planned to meet the special needs of the department. In 1931 Dr K. H. Tallerman, till then first assistant, was elected to the honorary staff of the hospital as assistant physician to the department. Dr R. W. B. Ellis was appointed to take his place as first assistant and registrar.

With the expansion of staff the activities of the department have been still further extended, and at the present time the work is carried on in the following manner

An out patient clinic works on four mornings a week. There is the care of twenty six inpatient beds for children up to fourteen years of age who are suffering from medical diseases. There is supervision and care of all infants in the obstetric nurseries. A follow up clinic is conducted once weekly for newborn infants delivered either in the obstetric wards or by nurses or students of the Hospital attending the mothers in their own homes (a regular part of the English obstetric training). The infants attend at this clinic until the age of two months, when, if progressing normally, they are transferred with a brief written report to the municipal clinics in their own district. These municipal clinics are responsible to the Ministry of Health for operating the national maternity and child welfare scheme, and have an organisation including home visiting by nurses, which is beyond the scope of hospital work in its ordinary sense. Infants who at the age of two months are considered to be in any way abnormal are not referred in this way to their local welfare clinics but are transferred to the ordinary sessions of the children's department, where they are treated until fit for discharge from hospital care. The relations with the above mentioned municipal clinics are very friendly, and our department acts as a consultation centre to these clinics, cases of difficulty being referred from them for consultative opinion and hospital treatment if necessary. There is in addition in the department a special clinic held once weekly for the investigation of breast fed infants who fail to thrive. At this breast feeding clinic there are facilities for test weighing the infant at three successive feedings, while the mother may spend the day at the clinic. The average amount the infant is taking thus becomes known and is reported to the physician at the next ordinary attendance of the mother and child, complementary feedings or adjustments of the feeding can thus be accurately estimated. At this clinic the mother also receives instruction in the technique of breast feeding, by the sister in charge. Finally, there is in operation a clinic for the treatment of speech defects, tuition being carried out by two specially qualified workers in this field. The department also acts in a consultative capacity to the School Medical Service and treats if necessary any children referred by the school medical officers, through the agency of a special secretary; reports on such children are sent back to them. A social service worker is allotted to the department, and great help is afforded in the out patient clinic by three or four voluntary workers.

A modified appointment system operates in the out patient clinic, and although it is impossible, especially on account of student teaching, to see each patient at an individually arranged time, patients are allotted times for the subsequent visit and are booked in advance to attend in batches at hourly intervals. Thus the amount of waiting to which they are subjected is cut down very considerably.

The laboratory facilities at the Hospital are extensive, and, although no laboratory is set aside solely for the use of the paediatric department, full investigation of any case can always be obtained, and accommodation is allotted for any member of the department wishing to carry out any particular research work. The published work of an experimental character which has emanated from the department goes to show that such facilities have been appreciated and utilised. In the same way all the other special departments of the Hospital—x ray, electrical, massage, etc.—offer every means for full investigation and treatment of cases and for consultation with colleagues engaged in other branches of medical work.

The mass of clinical material makes great opportunity for clinical research, and the facilities of the Hospital and the cooperation of members of the staff in other departments make this very fruitful. In recent years studies on the prognosis of nephritis and of obesity in childhood, on recurrent vomiting attacks in children, and on atelectatic bronchiectasis may be cited as examples of work of this character carried out in the department by members of its staff.

As one of the principal functions of a general teaching hospital is the training of medical undergraduates, it may be of interest to set out briefly the plan of paediatric teaching which is adopted. Instruction in regard to the infant and child is arranged to run concurrently with instruction in midwifery and obstetrics. During a two-month period in which the student is engaged in carrying out his practical midwifery he is given an elementary course in infant feeding receives instruction upon the newborn by means of ward rounds in the obstetric nursery conducted by a paediatrician, and further attends the infant follow up clinic, where he has the opportunity of seeing again the patients he has delivered and of noting their progress and the methods adopted in handling such feeding difficulties that may arise. It seems a logical and advantageous arrangement that he should receive such instruction while learning obstetrics. At this time also he is given a weekly demonstration of patients in the children's medical ward a preparation for his work as a ward clerk. During the three-month period following this, and while he is engaged also in gynaecology he is appointed a clinical clerk in the children's department as such he has allotted to him inpatient cases, of which he is expected to take a history make the necessary examinations, and keep subsequent progress notes. This is of course additional to the examination and notes of such cases made and recorded by the resident in-charge. During this period of clerkship the student attends a weekly ward round or demonstration conducted by the physician in charge of the department and attends at a teaching session in the out patient department conducted by the assistant physician to the department. A feature of the out patient session is the teaching on unselected cases attending the department on that particular morning. By this means students have the opportunity of seeing how ordinary cases coming to hospital for a first visit are handled, of observing the methods adopted for arriving at a diagnosis, of learning what investigations may be required in any particular type of case and, in fact of getting to realise how any particular medical problem is handled in the way they will have to handle it themselves later in practice. In addition to such formal teaching students are helped and supervised on their own cases in the ward by the first assistant to the department.

During their period of attendance in the department it is arranged that students also attend a few sessions at an infant welfare centre conducted by a municipal authority in order to gain an appreciation of the type of work carried out in such clinics, and to learn the methods of approaching infant management and feeding from a prophylactic standpoint.

Finally, a course of didactic lectures in paediatrics is held for the students during alternate winter sessions and before qualifying in medicine each student is required to have attended such a course.

Realising the impossibility of giving an adequate training in any special branch of medicine to men during their student period, the whole object of the paediatric teaching in the department is to give at any rate a comprehensive survey of paediatric work from all angles, with insistence upon the common problems in the subject which are likely to crop up continually in a general practitioner's experience. To those who wish for more complete training in paediatrics, clinical assistantships and later the resident post of house physician are available.

It is encouraging to find how large a number of students attend the teaching sessions in the department after the days of their compulsory clerkship are over. In this way these men who are always free to come to these sessions if they wish to supplement the statutory course which in the very nature of things is bound to be somewhat brief.

The department also takes its share in the postgraduate medical teaching of the hospital, demonstrations and lectures being given as part of a regular course held

twice in each year, any postgraduate attending the practice of the hospital is always welcomed in the department, should he care to attend at the ward rounds or the out patient teaching sessions

The case notes both for inpatients and for out patients are kept in a manner similar to that employed at all up to date hospitals, and call for no special mention, except that it may be noted that for out patients a folder system is adopted, and the case notes are comparable in completeness with those of the inpatients. They are never handled by the patients themselves, when an out patient is admitted to the ward, the case folder goes to the ward too, subsequently a summary of the inpatient notes is made upon it by the house physician when the patient is discharged. Continuity between out patient and inpatient notes is thus carried on in a useful and practical manner

Criticism is sometimes levelled against the rapidity and the apparently casual methods of examination seen in English outpatient clinics. When, for example, it is considered that a limited staff, in the department above described, has to deal with approximately 15,000 attendances, including 2,000 new patients a year, it will be realised that the full working up of a case becomes entirely a function of the inpatient department. In the outpatient clinic one is called upon to handle and to teach upon a mass of quite unselected material and to deal with it in the same way in which a practitioner must handle a busy practice, seeing those cases which on clinical grounds require further or special investigation and dealing with them accordingly. In our view such a method enhances enormously the clinical experience of both student and staff, and in actual practice it does not appear to be disadvantageous to the patients themselves

An attempt has been made in the above brief article to give an insight into the work and teaching methods of a paediatric department of a large English general teaching hospital. It was felt that such an account would be more interesting and more profitable than would be the case if attention had been centred chiefly upon any particular subjects of investigation being carried out in the department

in the sensitization experiments the skin gave a delayed response, and later it developed the immediate wheal and erythema as in the usual allergic (atopic) skin test. The production varied definitely with the dosage of serum but was produced just as easily in allergic as in non allergic individuals. Passive transfer of the skin test was successful in proportion to the intensity of the direct skin test. A second group of atopic individuals was sensitized by nasal administration. These experiments would seem most vital to anyone interested in theoretical discussions of allergy. While it is granted that serum sensitivity has certain differences from other types of sensitivity this study of its production in man suggests parallels with Rhus dermatitis and related 'contact' dermatoses in which the skin test is usually considered of no importance and the patch test specific. It further suggests the significance of 'delayed skin responses,' which many workers are prone to discount. It may signify that the patch test is simply a delayed skin reaction associated with a less intense sensitivity. The difficulty of studying direct skin tests for longer than a few hours is obvious yet those of us treating allergic patients have seen many instances where with definitely positive scratch test reaction by patch test is also striking. One might also conclude from this work that the indiscriminate injection of nonessential antigens (shotgun therapy) is not free from the danger of inducing sensitivity.

Somewhat in contrast with the work of Rackemaun and Simon²¹ Brunner²² found atopic individuals difficult to sensitize by subcutaneous injection of accepted allergens. He did, however, succeed in inducing a sensitivity to orris root, but it was of short duration. Perhaps the subcutaneous injection is not so efficacious as the intracutaneous route since the latter was used by Rackemann.

The peculiar rôle of the skin has been receiving considerable attention in immune as well as allergic phenomena. The study of virus immunity by Donnally and Nicholson²³ stressed the importance of proper skin inoculation. While the difference between allergic and immune processes is granted it is apparent that inoculation effects will vary with the involvement of the skin per se which fact is being used in many studies of bacterial products.

The study of nickel dermatitis suggests a link between pharmacologic toxic responses and the response to Rhus extracts. Stewart and Corman²⁴ produced a dermatitis in guinea pigs by percutaneous application of nickel salts. The reaction varied with the concentration of the solution (nickel chloride), produced no eosinophilia and was not influenced by preexisting protein sensitivity. Previous intradermal or intraperitoneal treatment made the skin more resistant. They discussed the various interpretations of their experiments.

An interesting and new view of the problem of food allergy was that of Oelgoetz²⁵ and his coworkers. They suggested that digestion started in the intestine and is completed in the blood stream. An excess of food and a decrease in pancreatic function might cause a relative reduction of the blood enzyme content in the hypersensitive. They proposed a test based on the blood content of free amylase before and after a standard meal. It is difficult to reconcile their hypotheses with earlier experiments in passive transfer²⁶ in which the allergens, given orally induced a positive skin test.

CLINICAL STUDIES

The inheritance of an allergic constitution was presented by Bucher and Keeler²⁷ through five generations of one family, consisting of 236 males and 218 females. With the allergic constitution apparently transmitted as a simple dominant unit character, male and female were affected in equal numbers. Asthma was manifested in 49 per cent, hives or eczema in 42.1 per cent, and there were multiple manifestations in 17.6 per cent of the family.

A discussion by J. F. Smith²⁸ of clinical aspects of "supersensitiveness" (note the term) convinced the reviewer that many of the British reports are inconsequential. Winnicott's²⁹ peculiar enthusiasm for a Freudian interpretation of urticaria was likewise not as impressive as some of our own ideas on the psychogenic factors in allergy. More enlightening was Rackemann's³⁰ review of phases of allergy. This article will be well worth careful reading by those interested in theory based on experience.

The new *American Journal of Digestive Diseases and Nutrition*³¹ will apparently be another source of information on food allergy. The first volume contained the Oelgoetz³² studies and in addition had a timely discussion of food allergy by Vaughan³³. He gave a general review of the status of food allergy and added a short paragraph on his new leucopenic index test. A preliminary report,³⁴ devoted exclusively to the leucopenic index, appeared later in the *Journal of Allergy*. Vaughan's first patient had abdominal pains, hives, and headaches following the ingestion of certain foods. In most instances there was an accompanying leucopenia within ninety minutes. He presumed that the ingestion of the offending food produced a mild protein shock which was accompanied by leucopenia as in anaphylaxis. He believed the leucopenic index is a valuable diagnostic adjunct.

Another report on food allergy by Rowe³⁵ discussed the rationale of the elimination diet. The reviewer has found some of his revised menus and new recipes of great value. There was a general symposium on food allergy by O. H. Brown³⁶ with his impressions.

The brief for allergic migraine was discussed in the preceding critical review³⁷. Opinions expressed by Andresen³⁸ in his article, "Migraine, An Allergic Phenomenon" in the new Journal, are in direct contrast to those of the reviewer. Andresen held for a definite organic cause of cerebromeningeal edema on an allergic basis. However, when he mentioned desensitization, removal of foci, and the restoration of a "normal endocrine balance," his thesis lost weight. An antidote for Andresen's discussion will be found in an editorial³⁹ of the *Journal of the American Medical Association*, "The Riddle of Migraine."

During the past year there has been an increased interest and many excellent reports on allergic dermatitis. Williams⁴⁰ in a comprehensive article on cutaneous manifestations of allergy, emphasized the distinction between the allergic and the immune response in the allergic phases of syphilis, tuberculosis, trichophytosis, and bacterial skin diseases. He followed closely Coca's terminology and pointed out the lack of inheritance factors and the necessity of previous contact in the dermatitis.

On the knotty subject of urticaria, the reviewer found the article by Hopkins and Kesten⁴¹ the most clarifying. They divided the external (contact) urticarias into toxic (pharmacologic) and allergic

The internal causes they listed as serum sickness food, drugs, inhalants fungi, bacteria, physical agents, insect bites, metabolic causes, and psychogenic factors. They mentioned the peculiar paradox of negative skin tests in cases in which clinical involvement of the skin was the only allergy. This has been observed by many workers but few have felt it to be unusual. Could this be related to a lessened state of sensitivity as in Rackemann's experiments in serum sensitivity? The peculiar fixed eruption sites of arsphenamine (drug) urticaria were also mentioned. Hopkins and Kesten successfully treated menstrual (metabolic-endocrine) urticaria by antoserum inoculation. An other interesting citation from their own work was the recovery of a patient with keratoconjunctivitis and adjacent urticaria upon removal of a rabbit hair from the eye. They devoted considerable attention to the rôle of bacteria in foci of infection, especially in the gallbladder. In summarizing the entire subject of urticaria, they concluded that skin tests were usually negative and elimination diets disappointing despite a fair proportion of food allergy in their group of patients.

Mendelsohn⁴² likewise discussed this question of sensitization tests and dermatitis and came to similar conclusions. He felt that positive reactions were often misleading as applied to the skin condition and that indiscriminate testing is not justified. He found the patch test of great value when external irritants were involved, but he emphasized the necessity of a proper history and dermatologic survey.

Walzer and Grolnick⁴³ shed some light on the occurrence of positive skin tests in papular urticaria. They found in such instances that other forms of allergy (atopy) were usually present and that the positive skin tests were referable to the latter and not to the dermatologic condition. They also demonstrated to their own satisfaction that skin tests were of little value in urticaria alone but did not comment on this paradox and dismissed it with the classification "nonatopic."

Here again the orderly mind of Coca⁴⁴ has given us a classification. He considered the various types of skin allergy to fall in three groups:

Technic of Test

- | | |
|-----------------------------|-------------------------------|
| 1 Atopic dermatoses | Intracutaneous |
| (familial occurrence) | Scratch or indirect |
| 2 Contact dermatitis | |
| (nonfamilial) | Surface contact or patch test |
| 3 Fungous dermatitis | |
| (eczematous dermatophytids) | Intracutaneous or patch |

The reviewer is glad Coca coined no new terms since much of the recent work has tended to discard some of his earlier classifications.

It was only a year ago that Sulzberger and his associates,⁴⁵ who follow Coca's terminology rather closely, claimed that silk sensitivity was often accompanied by a positive cutaneous test but its significance in dermatoses was open to question. This year he and Vaughan⁴⁶ reported a study of positive skin tests to silk with negative patch tests and claimed that the dermatitis resulted from inhalation of silk. While obviously not a true "contact dermatitis" this finding showed the danger of too early a pronouncement regarding phenomena and their classification.

Coca,⁴⁷ discussing allergic skin diseases, was encouraged by the reports of improvement in atopic conditions following surgical eradication of purulent infection. The rôle of infection in precipitating or aggravating "atopic" responses, does not seem new, and the implications of Bulky's⁴⁸ work, previously cited, are of definite importance. The reviewer has witnessed the swing from the radical program of surgical removal of tonsils and adenoids and antrum irrigations to the equally extreme refusal to allow removal of obviously infected tonsils because the patient was allergic. Perhaps we are now ready for the middle of the road. In any event, the study of bacterial toxin influences may be as important as the rather vain search for criteria of the "allergic constitution."

Coca mentioned the newer work of Sulzberger on silk sensitivity, though the reviewer would point out that this was first described by Figley and Parkhuist⁴⁹ and Taub and Zakon⁵⁰ at a time when Sulzberger⁵¹ considered silk dermatitis as only a contact response.

More justifiable is Coca's⁵² enthusiasm regarding Sulzberger's⁵³ work on the rôle of fungi in dermatitis. The latter showed skin test phenomena differentiating monilia and trichophyton infection and paved the way for therapeutic hyposensitization. Templeton⁵⁴ and others have already verified its clinical application.

Hill's⁵⁵ work on infantile eczema, however, is inconclusive. He found 15 per cent positive reactions to *Monilia albicans* in a group of patients with eczema and 8 per cent positive reactions in a control group. When the difficulties in testing young infants are considered, his results are not surprising.

Stiaus⁵⁶ has continued his researches on dermatitis venenata. In his earlier reports⁵⁷ there was the suggestion that sensitivity could be established by oral administration of Rhus extract. His 1934 reports showed that oral administration is not sufficient and that the contact or dermal route is essential. Spain, Newell, and Meeker⁵⁸ have also studied susceptibility to alcoholic extracts of Rhus. They found no apparent effect from first applications of the extracts.

White⁵⁹ found the ordinary skin tests of little value on acneiform dermatitis, yet food allergens were definitely responsible. Nonallergic trial diets were diagnostic and therapeutic. Ragweed dermatitis was studied by Brunsting and Anderson,⁶⁰ who found that the irritant was not limited to the oil fraction of the pollen (Coca) and that the almond-oil extract treatment of Gowen⁶¹ was difficult to evaluate. The reviewer feels, however, that in general this treatment of many of the similar dermatoses is very helpful. A case of cedar bark sensitivity was apparently benefited by the oil-cedar-extract treatment. Rowe⁶² reported the occurrence of camomile as a skin irritant resembling Rhus. Previous contact was apparently a factor, and its widespread occurrence added to its importance. The dermatitis attributed to socks was found by Schwartz⁶³ to be the action of the dye or the "finish," and washing removed or altered the irritating fractions.

Peculiar forms of light sensitivity were presented by Anderson and Ayers⁶⁴. They discussed hydia, vitiligo, and lupus erythematosus, the rôle of dyes, drugs, foods, and infections as sensitizing adjuncts and those little understood factors of sulphur metabolism and the significance of porphyrin.

"Another case" of urticaria by cold was reported by Dubbs⁶³. He was apparently able to control the symptoms by calcium administration but hoped to try hyposensitization by graded exposure or histamine injection in order to obtain more permanent improvement. The danger of allergic reactions following transfusion, was illustrated by the response described by Tedstrom⁶⁴. Far too frequently transfusions are given regardless of the possible factors of allergy.

A discussion of insulin allergy by Davidson⁶⁵ showed that even the most purified insulin is of an antigenic nature. He found sensitization was rare and the relation of this allergy to diabetes merely casual.

Spain and Newell⁶⁶ were able to show the presence of resins in blister fluid by producing blisters with cantharides. A number of passive transfers to a variety of inhalants were obtained.

Carey and Gay⁶⁷ reported on skin tests in infants. They found a variable reaction to histamine but no difficulty in obtaining passive transfer. They referred to Bell's⁷⁰ work but failed to mention the earlier work of Smyth and Bain⁷¹.

R. A. Cooke's⁷² article on asthma in children is, as usual, well worth reading. His paper covered causes, diagnosis, and treatment. He also discussed immediate as opposed to delayed clinical symptoms, but at the same time he felt that delayed skin tests were of no significance. The rôle of familial incidence, intruterine contact (placental transmission of Rstner), specific and nonspecific excitants were also discussed. He considered the pulmonary response in asthma one of edema rather than bronchospasm and felt that infective agents may act as foci long after the acute stage. The usual finding of food allergens in infants and inhalant allergens in older children was borne out in his experience. The reviewer was surprised at his recommending morphine for children during acute asthmatic attacks and the injection of food antigens rather than their avoidance. Likewise surprising was his endorsement of x-ray treatment rather than tonsillectomy for tonsillar infective foci. He stressed general measures and the anticipation of allergy in the young of allergic families.

Duke⁷³ reported soy bean as an excitant of allergy and discussed its action either as an inhalant or food allergen, its distribution and uses. His report is of interest in cases in which Sobee is a substitute for milk for allergic infants.

The standardization of pollen extracts has continued to be a much argued point. Coca⁷⁴ suggested that the Noon pollen unit be revised as 0.00001 mg of total nitrogen. Spain and Newell⁷⁵ studied the effect of ultrafiltration of ragweed pollen which separates protein nitrogen and nonprotein nitrogen fractions. They concluded that the phosphotungstic acid precipitable nitrogen (standardization method of Cooke and Stull) did not correspond exactly with the allergic activity but was still the most practical method. On the other hand Bowman⁷⁶ found by biologic assay (skin test) that the standard of Cooke and Stull was fallacious. The reviewer feels that too fine a standardization may not be warranted at the present time and either standard is practical.

Moore and Unger⁷⁷ concluded that the pollen allergen must be of a protein nature because of its susceptibility to enzyme digestion.

Pollen surveys were made by Barrett,⁷⁸ working in the Utah region, by La Rush⁷⁹ in Toronto (1932), and by Lamson and Watry⁸⁰ in northern Arizona

Dushan and Cohen⁸¹ proposed a puncture method for skin tests which they found superior to the usual type of abrasion. In studying pulmonary and dermal tests of sensitivity to inhalants, Stevens⁸² found no greater reliability in the former than in the latter. They were unable to confirm any local specificity of tests by the use of spray applications and concluded that the test-negative group remained about 50 per cent of the total. Rudolph and Cohen,⁸³ however, in their report on vasomotor rhinitis with negative skin tests found a local nasal test helpful. Their application was by pledget which suggests a mucous membrane test comparable with the local patch test for dermatosis. They considered the condition a local allergy. If their test is a delayed response, the reviewer wonders if patch test to the skin might be positive or if they would suggest an oil-extract hypersensitization, such as has been advocated for "contact dermatitis." It would also appear difficult to control nonspecific effects in their "pledget" tests. Somewhat parallel was the suggestion of Forman⁸⁴ that while vasomotor rhinitis is as a rule "atopic," there are a few instances where skin tests are negative and a contact "coryza" exists. He had a diagram for aid in studying these nonreactors. The conjunctival test was found less sensitive than the skin test by Simon.⁸⁵ His case report seemed most unusual. The patient had vasomotor symptoms and was sensitive not only to horse serums but also to all mammalian serums. Passive transfer was obtained. He thought his case illustrated a common denominator in the various serums. If such conditions are more prevalent than is commonly supposed, reactions from the antitoxins from sources other than the horse can be explained. In reference to horse dander and horse serum sensitivity, he considered the condition acquired. He found certain horse-sensitive asthmatics might tolerate antitoxin. He advised conjunctival as well as skin tests before administration of therapeutic serum.

In the field of treatment, Brown⁸⁶ continued his enthusiasm for massive pollen therapy. He did not consider the method to be particularly dangerous although some of us dealing with children would hesitate to adopt such a program for general use. In this respect the report of Lichtenstein⁸⁷ on the use of intravenous pollen therapy was startling to say the least. He did not think the method dangerous and found a resultant definite depression of the skin test though the blood contained ample circulating reagin. Considering the usual caution which the reviewer has felt necessary for pollen injections and the occasional severe reaction in spite of precautions, he wonders if Lichtenstein has yet to encounter episodes likely to modify his present opinion.

Waldbott and Ascher⁸⁸ have also studied rapid hyposensitization with the conclusion that the method is not without danger but can be used in certain urgent conditions. Moore and Unger⁸⁹ compared dextrose pollen extracts with those in a glycerin vehicle. Results in treatment were similar, but dextrose solutions were less painful and easier to handle. The reviewer wished for more comment on the relative sterility of the two solutions. Unger and Moore⁹⁰ believed that perennial was better than preseasonal treatment. Walker,⁹¹ on the contrary, felt that preseasonal treatment of hay fever with proper pollen ex-

tracts, offered permanent relief. As a rule however three to six courses of such treatments were necessary, and in such instances an average of 75 per cent of those treated were relieved.

Rappaport and his coworkers⁸² considered viosterol of definite value when used with the specific treatment of hay fever and that the latter alone was not so efficacious. They suggested not a calcium effect *per se* but a potassium calcium ratio control. Rappaport has been persistent in his advocacy of viosterol. It is a matter of conjecture what undesirable effects might be obtained by continuous use of very concentrated vitamin D.

Some peculiar phenomena of allergic nature have been reported during the past year. Massy and Gilmore⁸³ described a violent reaction to the Schick test given for the third time. Toxoid had been used previously, and the serum titer showed immunity to diphtheria. The instance was obviously one of sensitization. Cole and Korns⁸⁴ described visceral manifestations of angioneurotic edema and considered the pulmonary symptoms Quincke's edema of the lungs. Waldhott⁸⁵ discussed shock reactions from substances other than pollens and serums. He likewise attributed the reactions to a sudden edema in various parts of the body. These reports of Walcott on allergic death should check any enthusiasm for procedures such as have been already discussed with reference to Lichtenstein's intravenous pollen therapy. With Ascher, Waldhott⁸⁶ reported a neuropsychiatric reaction which simulated these allergic shock conditions and pointed out the difficulty in differentiating "asthma nervosa."

Harkavy⁸⁷ has continued his observations on tobacco sensitivity in relation to thromboangitis obliterans. In normal smokers he found parallel reactions between tobacco leaf and pollen i.e. allergy with multiple sensitivity. In patients with thromboangitis obliterans reactions to leaf alone were characteristic. With Romanoff⁸⁸ he substantiated his earlier claims⁸⁹ by reporting 69 per cent positive reactions to tobacco in patients with thromboangitis obliterans, while only 11 per cent were positive in the control group. Suggestive of Vaughan's leucopenic index in food allergy is the report of Squier and Madison⁹⁰ of primary granulocytopenia due to hypersensitivity to amidopyrine. It will be interesting if this cytologic finding proves characteristic of many ingestant allergies. Frumess⁹¹ report on allergic reactions to dinitrophenol added a new drug to the list of potential allergies and suggested the need for caution with regard to its use.

A further study of Caddis fly allergens by Osgood⁹² pointed to the existence of one factor common to both species of the fly while an additional allergen was confined to one of the species. Fisher and Center⁹³ reported successful treatment of 'bee' sensitivity with whole bee extract. This of course, is a further verification of Benson's⁹⁴ work previously discussed. Considering the occasional instances of sensitivity to that well known insect of San Francisco the reviewer takes courage to apply this treatment for flea sensitivity. Those who rely on the use of pyrethrum insecticides for such conditions will find the comprehensive discussion on pyrethrum sensitization by Fineberg⁹⁵ most helpful. From his own observations the reviewer can speak with feeling on Eastern visitors who, sensitive to ragweed attempt to use substances containing pyrethrum to combat the San

Francisco flea The result is not unlike the proverbial jump from the frying pan into the fire Taub¹⁰⁶ has likewise given a rather full report of the widespread uses of cottonseed Found as an ingestant, contactant, and inhalant, cottonseed assumes a rôle of major importance in those sensitive to the substance

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American Academy of Pediatrics

JOHN RUHRAH

1872-1935

JOHN RUHRAH, of Baltimore, Md., a widely known and much beloved pediatrician, died at Mercy Hospital, Baltimore, March 10, 1935. He was born September 26, 1872, in Chillicothe, Ohio.

In October, 1930, after attending the International Pediatric Congress at Stockholm, he suffered an attack of poliomyelitis from which, after a long siege of illness, he recovered sufficiently to enable him to resume his practice, also to travel, and to engage in many of his lifelong activities, though a residual paralysis of his lower extremities persisted. About two months ago, while examining a patient in his office, he was suddenly attacked with what appeared to be an apoplectic seizure. He was removed to Mercy Hospital on January 17, 1935. His mind was clear almost to the last, and during his final illness he retained that fine humor and stoicism which had characterized his whole life.

Ruhráh was graduated from the Chillicothe High School in 1891 and received his medical degree from the College of Physicians and Surgeons, Baltimore, 1894. He took postgraduate courses at Johns Hopkins Hospital Medical School, at l'Institut Pasteur in Paris, 1897, and at the universities and hospitals of Vienna, Berlin, and Paris, 1900, 1901. He was assistant resident physician at Mercy Hospital, 1894, 1895, and resident physician, 1895-1897. He was physician in charge of the Pasteur Department of the College of Physicians and Surgeons, 1897. From 1898 to 1900 he was quarantine physician at the port of Baltimore. At about this time he was appointed to the chair of diseases of children at the University of Maryland Medical School, a position which he held for many years. He was also visiting physician to the Mercy Hospital, consulting physician to the Church Home and Infirmary, and visiting physician to the Hospital for Women of Maryland.

He was elected president of the Medical and Surgical Faculty of Maryland in 1919, President of the American Pediatric Society in 1912, president of the Medical Library Association in 1927, president of the Research Society in 1932, president of the Osler Historical Society in 1933, and president of the American Academy of Pediatrics in 1934. He was a member of the Board of Education of Baltimore. In 1932 he was selected by the Baltimore City Medical Society to prepare a history of the medical profession in Maryland for the last quarter of a century, a task which he was well qualified to perform. He entered private practice in Baltimore in 1901 though he continued his academic connections, teaching bacteriology, pathology, and clinical medicine in the College of Physicians and Surgeons. He never married.

He was a facile writer. His style was terse, with occasional shafts of fine humor, and his wide reading in many languages manifested itself in his numerous pertinent references from many fields of literature. Among his books may be mentioned *Diet in Health and Disease* (with Julius Friedenwald), sixth edition, 1925, *Dietetics for Nurses* (also with Friedenwald), fifth edition, 1924, *Manual of Pediatrics of the Past*, 1925, *Pediatric Biographies*, 1932, *William Cadogan*, *His Essay on Gout*, 1925, *Poliomyelitis in All Its Aspects* (with E. E. Meyer),

1917 He contributed articles on pediatric subjects to most of the modern American encyclopedias and systems of medicine among which may be mentioned Osler's *Modern Medicine* Nelson's *Living Medicine* Tice's *Practice of Medicine* and Abt's *Pediatrics*. Rubr h made the first collective investigation of actinomycosis in the United States, 1899 1900, and he introduced the soy bean in infant dietetics, 1909.

One of his impelling interests was his love of books, which showed itself in his passion for the study of "the old worthies" in the pediatric literature. During the past several years he has been a regular contributor to the *American Journal of Diseases of Children* on the subjects of pediatric biographies and pediatrics in art. His biographic sketches refer to interesting pediatric writers of the past and his art



sketches, to reproductions of interesting illustrations of various phases of child health and hygiene. He sometimes was given to writing verse, and at medical meetings he would become inspired to write a few stanzas suggested by the themes under discussion, in which he would humorously reduce the highly involved scientific presentations to common-sense interpretations. His poem on infant feeding became famous.

Rubr h had a matchless personality and a great facility for establishing enduring friendships. He had a charm and graciousness of manner which led one to feel at home in his presence. He was extremely tolerant. He forgave shortcomings and appreciated even the minor virtues of his fellow men. He mingled well with all classes of people. The lowly and untutored did not repel him, and he met the intelligentsia gracefully and with exceptional poise. He was a brilliant conversa-

tionahst, scintillating and entertaining He was always reminded of a choice tale from a rare book or a forgotten author It was a treat to enjoy his companionship during a leisure hour

His artistic tastes were not confined only to art and literature He was also a devotee of fine music It was said of him in Baltimore that he scarcely ever missed a worth while musical event at the Lyric Theater He made the annual pilgrimage to Bethlehem, Pennsylvania, for the Bach music festival, which he spoke of to his friends as one of the most important events of his year On his numerous trips to Europe he made it a point to visit one or more of the summer music festivals.

Ruhrah lived a full life He combined the activities of the practitioner of medicine with a large degree of human understanding and common sense He had an artistic nature which craved the cultural things in life These he found it possible to provide for himself After his severe affliction, by undaunted courage and indomitable will, he was happily able to resume his work and his recreations He gradually took on new tasks and carried on with joy and zest until the final illness John Ruhrah leaves a rich heritage of devoted service dedicated to medicine and humanity

“A man beloved, a man elect of men ”

—Swinburne

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Proceedings

FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

JUNE 11, 12, 1934

Round Table Discussion on Disorders of the Blood

Leader Dr Thomas B Cooley, Detroit, Mich

CHAIRMAN COOLEY —It is my purpose to bring up for discussion today some points regarding the general and therapeutic of anemia prefacing this with a few remarks on the structure of the red cell.

We know really surprisingly little about the make-up of this highly important cell. Even the traditional beginning of all descriptions of it that it is a biconcave disk, has been questioned and it has been likened rather to a saucer or a rubber ball with the air squeezed out. The familiar conception is of a limiting membrane of some sort enclosing a stroma, in which the hemoglobin is deposited. This stroma has been thought of as a spongy mass, or as a sol or gel, which might ooze out if the cell were damaged, while it has been assumed that the limiting membrane is chiefly protein. Though analyses are somewhat uncertain because of difficulties in removing all the hemoglobin such analyses as we have indicate that there is not enough protein in the cell structure to form a membrane more than two molecules in thickness. It is known that a considerable part of the cell is composed of lipids formerly supposed to be chiefly cholesterol and lecithin, though now cephalin is believed to be present in important amounts. It is probable that these lipids form a part of the membrane. They may be deposited in the interstices of a loose protein network or may form a layer either on the outside or the inside of the protein framework. The lipid mixture seems to have colloid properties which would vary if the relative proportions of the lipids were altered, and it has been suggested that something of this kind might account for changes in the permeability of the membrane. Certainly the cell's lipid content may be supposed to have a good deal to do with the types of hemolysis due to fat solvents. It is by no means certain that the hemoglobin is contained in the interior of the cell, and there are some good reasons for thinking that it may be deposited in the membrane, perhaps in the lipid layer in which case the interior of the adult cell, after the loss of the nucleus, would contain only fluid derived by osmosis from the plasma.

Whatever one's conception of the physicochemical structure of the cell may be, it seems evident that the cell structure must vary considerably under certain disease conditions. The remarkable changes in shape which the cells undergo in sickle-cell anemia, for instance, must depend on abnormalities of structure and it is easy to believe that the excessive destruction of the cells in some other anemic states is a result of structural defects or peculiarities.

THE ONTOGENESIS OF ANEMIA

Anemia is a condition in which the proportion of hemoglobin in a given volume of blood is less than normal. This hemoglobin deficit may or may not be accom-

pamed by a lowering of the red cell count, on the other hand, if the cell count is markedly lowered, there will of necessity be a hemoglobin lack also

Whatever the fundamental cause of the state may be, the actual production of anemia can be only by some one of the following

- 1 Direct blood loss
- 2 Failure of red cell production or maturation
- 3 Excessive cell destruction
- 4 Failure of hemoglobin formation
- 5 Combination of two or more of the above factors

Direct Blood Loss—The mechanism of anemia production from this cause needs no special comment

Failure of Cell Production—A. Marrow Hypoplasia By this we mean a condition in which the erythropoietic activity of the marrow is for the time being partly or wholly suspended Capacity for function remains, however, and when the cause of the hypoplasia is removed, normal function returns.

Such a state seems to be an important factor in many of the secondary anemias, especially those arising in the course of infections, in which it may be supposed that the toxins of the infections have a depressant effect on the marrow It may be assumed to occur in conditions of under or malnutrition, in which the general metabolism is below par, or in which special metabolites which stimulate hemopoiesis are lacking It is apparently a factor in some of the anemias, precise etiology and pathogenesis of which are little understood

B Aplastic States Marrow aplasia may be said to be a condition in which so much of the active marrow is atrophied or destroyed that cells sufficient for the body's needs can no longer be produced. Poisoning by arsphenamine, benzol, etc., may have such an effect, as may physical agents, such as x ray and radium. Certain infections may have it as a sequel Prolonged hypoplasia may finally result in marrow atrophy In certain, probably constitutionally susceptible, individuals the anemia of hemorrhage may be followed by aplasia Prolonged sepsis is one of its rather common causes The type of aplasia which results from infiltration of the marrow by pathologic tissue, as in leucemia and malignant disease, is often spoken of as "myelophthisis."

Aplasia affects both erythropoietic and leucopoietic tissue and is characterized by progressive disappearance of all types of marrow cells from the circulation, without signs of regeneration.

C Lack of Structural Material The idea that in certain conditions red cell production is interfered with because the marrow is not being furnished with material necessary for the construction and normal development of the cell body is, in the present state of knowledge, largely a matter of inference from the effect of certain therapeutic procedures From what has been said of our meager knowledge of the cell structure, it is evident that this must be a difficult thing to prove, but the fact that the erythrocytes in some diseases have an obviously abnormal structure argues for the probability

Abnormal Destruction—Excessive erythrocyte destruction is an important feature of many of the anemic states In the "primary" constitutional hemolytic disorders the marrow apparently produces cells of defective structure, which are more readily affected by the destructive processes than is the normal cell.

Infectious states often produce a picture of increased destruction, usually by an exaggeration of the normal process of fragmentation As hypoplasia is also common with infection, these two processes may be found combined In such case the destruction usually ceases with the infection, while the hypoplasia may persist for some time after The reason for the increased fragmentation is not clear The toxins of infection might be supposed to act upon the marrow to cause it to pro

duce defective cells which break down easily, or they might act upon the formed cells to make them more fragile. As compared with this process of fragmentation, such hemolysis as goes on in hemolytic icterus under the influence of the spleen probably has little importance in the ordinary secondary anemias, nor is extensive phagocytosis of whole red cells a common phenomenon, though it is possibly of importance in some of the constitutional anemias.

Failure of Hemoglobin Formation—Iron is not the only important constituent of the hemoglobin molecule. The pigment radicle, with its pyrrol nucleus, and the amino acids which go to make up the globin fraction must be taken into consideration also. It is only recently that it seems to have been shown that the body is capable of synthesizing the pyrrol nucleus, which it had previously been supposed we must get from outside. These constituents other than iron have received a good deal of attention in recent years, and, while we must still believe that iron is the chief factor to be considered in defective hemoglobin synthesis, the success of therapeutic methods aimed at supplying other 'building stones' indicates clearly that in many cases it is not the sole or indeed the chief lacking ingredient. Some of the substances, such as copper and the vitamins C and G, which are believed to be important to hemoglobin synthesis, do not actually enter into the hemoglobin molecule but must act in some way not perfectly obvious to determine the reaction.

Combinations of Two or More Factors—These are common. In fact, there are probably few anemic states in which any one of the factors mentioned is solely responsible.

Hypoplasia and increased destruction are often associated in the anemias due to infection.

Recurrent bleeding may result in aplasia, while the aplastic state commonly causes hemorrhage.

Long-continued bleeding may so deplete the body's store of blood building materials as to cause a 'deficiency anemia,' in which more than one of the essential building stones may be lacking.

The purest type of anemia should be the form of 'nutritional anemia' due to depleted iron reserve, but even here infection sooner or later is likely to complicate the picture by introducing a hypoplastic or a hemolytic element.

THERAPEUTICS

Our therapeutic efforts must of course be based, in the given case on our conception of the pathogenesis and on the ability of the various items in our armamentarium to meet the apparent indications. For our present purpose the best method of approach to this question is probably to consider individually the various procedures in vogue and what we know of their applicability in the different anemic states.

The Uses of Iron—There is no question that iron still holds first place among the antianemic medicaments, and for more than one good reason. In many anemias, particularly those of premature infants and twins, there is good reason to think of a probable exhaustion of the stored iron which by all evidence can be more rapidly replaced by oral administration of suitable iron salts than by feeding of iron containing foods. In all of the hemolytic anemias there is more than the normal loss of iron from the body, and there is also a need for a resynthesis of hemoglobin to replace that destroyed. While the iron of the destroyed cells is probably largely used over again, we have no definite evidence as to the rapidity with which this process of reutilization goes on, and it seems only common sense to be sure that the hemopoietic tissues are assured of a proper supply of this important part of the hemo-

globin molecule Theoretically, the only anemic processes in which iron could be said not to be indicated would be those (hypoplasia and aplasia) in which the marrow is unable to utilize it There was a very general loss of faith in the efficacy of iron until the present tendency to give very large doses, since when it seems to have come into its own again. More than one reason is suggested for the efficiency of these large doses, many times greater than any possible need for hemoglobin synthesis A time honored one is failure of absorption, a reason which certainly has some force Whipple believes in a possible "salt action," as to the nature of which he is not very clear A recent idea is founded on the experiments with copper Practically all of the iron used contains minute amounts of this metal, and it is not impossible that the very large doses of iron are effective because they are the means of administering copper in sufficient amounts.

Some recent work has been done on the availability of different iron compounds It seems to be quite generally agreed that the organic preparations are the least useful and that the best are the inorganic salts already in solution, or readily dissolved by the HCl of the stomach The Wisconsin workers found the pyrophosphate especially good Parsons cites some trials supporting Heubner's contention that the ferrous salts are better than the ferric compounds. In this country iron and ammonium citrate and, for children, the saccharated carbonate are favorites.

Parenteral injection of iron, by one route or another, has had considerable vogue It has the apparent advantage that one need not reckon with uncertainty of absorption, but we have been unable to see that it has anything else to recommend it, as it is neither more reliable nor more rapid in its effect

Copper—The demonstration by the Wisconsin group that the addition of small amounts of copper to iron preparations is of great value in treating anemias of experimental animals has aroused much comment Some competent hematologists are not convinced that these findings are applicable to humans, but the tendency to add copper seems to be spreading In our own experience we have thought that the addition of copper enabled us to get results with smaller doses of iron, though this is not always true, and we not uncommonly find that we achieve this same effect more readily with liver, even in what seem to be simple iron deficiency anemias.

Inasmuch as copper is not a component of the hemoglobin molecule, it is assumed that its rôle is that of a catalyst

Liver—The use of liver, in the form either of the cooked meat, or of extract of whole liver, has grown greatly in the last few years, thanks largely to the work of Whipple, there can be no doubt now of its value The special extract used in the treatment of pernicious anemia is of little service in the ordinary anemias, and, according to some investigators, there are conditions in which the cooked flesh is more effective than any extract.

- Liver seems to have its chief value in those types of anemia in which there is need for new cell building, rather than in those in which there is simply a hemoglobin deficit, though there are indications that at times it furnishes something needed for hemoglobin synthesis There are many evidences that the liver is both factory and storehouse for materials of blood building It is the source of several of the factors in the clotting mechanism, it is the infant's storehouse for iron and copper and the principal place of deposit also for the pigments resulting from blood destruction, it is a fair deduction from its observed therapeutic effects that the liver furnishes other still unidentified substances that go to red cell building and development One of Whipple's experiments, in which he fed to his dogs the livers of patients who had died in various anemic states, showed that in some of them there had been a tremendous storage of blood "building stones," presumably because the marrow in these diseases had been unable to use them. Whipple has been able to show that iron and liver often have a remarkable complementary action, such that

the effect of the two given together may be more than the sum of their individual effects. It is rather a common observation, when both cell count and hemoglobin are low, that the giving of liver alone causes an increase in the cells while the hemoglobin lags until iron is added. Sometimes if iron alone is given first, precisely the same sequence is observed, with the liver giving the final stimulus to hemoglobin deposition. This is not so easy to explain. The idea, quite generally accepted for the effect of liver in pernicious anemia, that it furnishes a "maturation factor," can hardly be applicable in all of the types of secondary anemia in which it is found effective.

Marrow Extract—Theoretically the red marrow should contain practically every thing that goes to the building of the cells, and an active extract should be a useful addition to antianemic preparations. We have made considerable trial of one extract, and, while we have at times thought that we were getting some benefit from it, our results were not wholly convincing. Whether a different preparation or larger doses might work better, we cannot say. We have also tried the extract of yellow marrow used in some clinics for a supposed stimulus to white cell formation, with no perceptible effect.

Splenic Extract—This has the weight of Krumphhaar's recommendation, its use being based on a supposed regulatory of splenic products on the marrow. We have had little experience with it. It is a constituent of some proprietary preparations.

Amino Acids—Since the globin portion of the hemoglobin molecule and the protein framework of the cell must depend on essential amino acids for their synthesis, it is natural that trial should have been made of some of these substances in therapeutics. Injections of histidine, arginine, glutamic acid, and tryptophane have been used, and some good results have been reported. These reports are not wholly convincing. But since the work is still in the experimental stage, it is not at all improbable that something definite may come of it.

Vitamins—There are no characteristic anemias recognized as due to vitamin lack. There is evidence that vitamins C and G are essential to normal blood building, but even scurvy does not always cause definite anemia. It would seem probable, however that the disturbed metabolism accompanying any vitamin lack might well result in a secondary hypoplastic anemia, and it would be only common sense to correct any such deficiency. Occasional anemias are cured with no further treatment than this.

Diet and Hygiene—It is generally recognized that the "iron deficiency" anemia due to exhaustion of the iron reserve can usually be prevented, and sometimes cured, by timely introduction of iron-containing food in the diet. This is a precaution to be taken particularly with premature infants and twins when such an anemia has developed it is, of course, important. Information as to other specific dietary needs is not so clear. Liver is commonly included in antianemic diets and sometimes seems more effective given in this way than as an extract. Kidney according to Whipple is nearly as good. Red meat ranks high in the list of blood building foods. Eggs have always been rated high. Some of the vegetables long touted for their iron content, such as spinach have not been proved to have special value, while peaches and apricots are given high rank. On the whole, the requirements of an antianemic diet, so far as we know them now are that it should be as liberal and varied as the patient's age permits and should contain a generous proportion of the things known to favor blood building. The idea once prevalent that milk tends to produce anemia and should be excluded has disappeared. Its effect is bad only when it is used too long to the exclusion of other foods.

The need of sunshine and fresh air is not to be forgotten. One meets occasionally with mild hypochromic anemias which in our northern winter climate are refractory to all medicinal treatment, but which are cured promptly by transfer to the South.

Transfusion—A long list might be compiled of the conditions in which transfusion is supposed to be helpful. So far as the anemic states are concerned its most definite effect is the rapid replacement of cells, and, in the anemia of hemorrhage, of plasma constituents as well. It seems probable that besides furnishing cells to carry on normal oxygen metabolism, it also, by raising the general metabolism level, helps the marrow to function better, and thus may be looked upon as a stimulus to hemopoiesis. It must furnish some blood building material which may be needed. As the most reliable method for checking bleeding when the clotting mechanism is at fault, it is a preventive of increasing anemia in these conditions.

It is often a question when a given patient is in need of transfusion. It is true, in general, that the patient whose hemoglobin has fallen rapidly does less well at the same hemoglobin level than one with a more chronic type of anemia, who has gradually become accustomed to it. Thus one whose hemoglobin has fallen rapidly to 6 or 7 gm. may be in more urgent need of transfusion than one in whom it has declined gradually to 4 gm. While it is difficult to say, except in case of severe hemorrhage, just when a transfusion is necessary to recovery, it is often obvious that timely transfusion will greatly hasten the process, and it is usually wise, in grave anemias, to inaugurate treatment in this way rather than to wait for the effects of medicinal measures, which will be useful when transfusion has put the patient in better position to take advantage of them.

There has been some difference of opinion as to the duration of life of the transfused cells. We were able to study this over a long period in one case and to satisfy ourselves that the average life of the cell after transfusion was from two to three weeks. This does not, of course, mean that the total life of the cell is not considerably more than this.

There is no question that the intravenous method of transfusion is the most satisfactory. Intraperitoneal injection has a slower, less sure effect but is useful for repeated doses when there are obstacles to the intravenous technic. The discussion over relative merits of citrated and noncitrated blood is of little importance. Theoretically the noncitrated blood is better when the platelets are needed.

Intramuscular injection of blood does not furnish red cells to the circulation. Blood given this way does furnish plasma constituents, which may be utilized by the marrow, and products of cell disintegration, which by a chemotactic effect may be stimulant to hemopoiesis.

Josephs has recently shown that in certain of the hemolytic anemias the injection of concentrated plasma has an effect closely paralleling that of transfusion in the same disorders. This must be due to its furnishing some essential building stones for which it is the normal carrier.

Splenectomy—The vogue of splenectomy is growing steadily. It is being tried now in a wide variety of conditions, in some of which the indications are rather vague, and the results are not yet convincing. We are concerned here only with what may be expected of it in anemic states. Its chief indication seems to be to put a stop to a pernicious activity of the spleen, which is most readily denominated, in the lack of a complete understanding of its nature, as "hypersplenism." Since this condition lies at the bottom of the type of hemolysis met with in hemolytic icterus and apparently in erythroblastosis of the newborn, removal of the spleen almost invariably puts an end to it, as this particular splenic activity seems not to be readily taken over by other depots of reticuloendothelium.

The two conditions in which it has scored its most marked successes are hemolytic icterus and hemorrhagic purpura, in both of which it may be said to be almost a certain cure, its success in these diseases is an important point in the reasoning as to their pathogenesis.

There are no other anemic states in which its results are so striking. It has been practiced in many, perhaps most, of the recognized cases of erythroblastic

anemia, merely to rid the patient of the burden of the greatly enlarged spleen. It does not appreciably affect the disease process, though possibly the patients live somewhat longer than they would otherwise. In sickle-cell anemia we have found that we can mitigate the abdominal crises and perhaps the joint symptoms, by the operation, but the anemia is little changed. It is generally believed that in 'splenic anemia' early splenectomy lessens the probability of development of hemorrhage and cirrhosis, which are the later stages of the Banti syndrome. Unfortunately, this effect cannot be definitely depended upon. If one accepts the idea that the spleen normally exerts a control over marrow activity which may be perverted in some states, there might be an argument for splenectomy in obstinate hypoplasia which threatens to go on to aplasia.

One is often questioned as to possible deleterious effects of the operation. It is really remarkable that so important an organ can be removed with so little apparent effect upon the general body economy. The explanation must lie in the readiness with which the rest of the reticuloendothelium takes over the splenic functions. Just how serious the loss of the splenic reservoir might be in time of stress can hardly be estimated.

It has been generally accepted that it is dangerous to remove the spleen during a hemoclastic crisis, and in most clinics, certainly it is the custom to endeavor to carry the patient over the crisis and operate at a more favorable time. Since emergencies will arise, however, in which operation seems imperative with the improvements which have come in technic, the results of these emergency operations may prove less discouraging.

Some Practical Points—The management of the ordinary case of secondary anemia is a matter of good hygiene, proper diet, and a selection of pharmaceuticals to meet the indications. One must always remember however that in the commonest form of anemia, that due to infection, medicinal treatment is notoriously ineffective as long as the infection persists. If the condition is serious, frequent small transfusions may be needed both to counteract the anemia and to help the patient to throw off the infection and break the vicious circle.

As to pharmaceuticals—in the clinic it is of interest to experiment with various combinations of iron, liver, copper, etc. The private practitioner, whose main purpose is to achieve prompt results, will usually do better with some one of the "shotgun" preparations which are now met with in abundance. The most important ingredients to be looked for are iron and liver extract. We use for routine treatment a combination of iron, copper, and liver and marrow extracts which in varying dosage answers practically all our requirements. None of the liver extracts are especially palatable, and it may require some ingenuity to get the child to take them. For older children they may be had in capsules.

There is at present a great deal of discussion as to the desirability of adding iron to the food of all young infants—based largely on the work of Dr. Helen MacKay. We are not yet convinced of the need of this with children of good stock living in favorable surroundings, and the present evidence is that with premature infants and twins, in whom early anemia is especially likely to develop, neither iron nor liver can be depended on to forestall this.

DISCUSSION

DR. ARTHUR ABT (Chicago)—I have enjoyed Dr. Cooley's presentation immensely. His etiologic or causative classification reminded me of Czerny's classification of the nutritional diseases. It is the most difficult classification to make because there are so many mixed types. Personally I am not so brave. If I have a case of anemia during or following infection I put it in the clinical group of infectious anemias. If the infection prevents the child from taking proper diet or

perhaps from assimilating the diet, we call that the "alimentary infectious type" When the clinical basis for the anemia is simply an improper or unbalanced diet, I should call it an "alimentary anemia"

Dr Cooley has made us realize how little we really know of the physiology of the red cell, when even so simple a thing as its shape has been in doubt.

The resistance of the red cell is an interesting thing I think Goldbloom, of Montreal, showed that the resistance in the newborn infant is less than that of the older child We know very little about the mechanism of this greater or less resistance Dr Cooley's idea that it may have to do with the lipid structure was new to me

Some have thought that the infant during the first year may have a different kind of hemoglobin than the older child Horwitz found a difference spectroscopically between the blood of infants and that of older children

DR COOLEY—I was not trying to classify the clinical types of anemia, but the factors in pathogenesis, quite a different matter We classify our anemias clinically much as you do

I might say a word further as to the possible relation of the lipids to resistance It is rather striking that the most active hemolytic agents we have are things, such as saponin and ether, which would be more likely to affect the lipid than any other part of the cell Bechhold, as far as I know, was the first to suggest the probability of variations in the absolute and relative proportions of the different lipids in the cell and their possible relation to the cell's permeability There are not as yet any good analyses of the lipids in pathologic states

DR COOLEY (In reply to several questions)—The makers of a rather well known proprietary preparation have been furnishing us with the separate ingredients in the menstruum which they use, and we have experimented with various combinations The preparation itself, containing iron, copper, and liver and marrow extracts, is put up in both fluid and capsule form, we have found it very suitable for routine use in the clinic

Josephs' prescription of iron and ammonium citrate with 0.5 per cent copper sulphate is usually all the treatment needed in a pure nutritional anemia, and even in a severe case it is exceptional that one is unable to bring the hemoglobin to normal in four or five weeks by this treatment We lay stress on the time element because we do not think it a good thing for a young child to remain anemic any longer than necessary during this period of rapid growth I have never quite understood the interest of some of my friends in methods of treatment which take months to manifest their effects It is for this same reason that in any severe case, unless it be of a simple type which is sure to respond rapidly, I like to begin treatment by transfusion

DR FRANK NEFF (KANSAS CITY, MO)—It has come to the stage where we don't know what to do with the detail men who come in with preparations for the treatment of anemia

Recently we had a child with polycythemia and hyperchromia from too much transfusion. I wonder whether you have seen anything similar from any of these wonderful preparations

DR COOLEY—There are occasional reports of the production of polycythemia even from the administration of iron. That is difficult to explain theoretically When we began to try bone marrow, we fed it to some of the laboratory technicians. One girl had a hemoglobin of 17 gm. at the beginning of the administration, and after a few weeks it had risen to 21 gm. That is our sole experience

As to the effect of certain elements in the diet—it seems to me that we do not have any definite basis for estimating this precisely It has long been recognized

that occasionally one can get better results in the treatment of a nutritional anemia by changing from a poor diet to a good one than by any drug administration. There has been, as you know, a good deal of study of the vegetables, especially with reference to their iron and copper content, though there is probably more to it than this. Practically nothing is known of the value of the cereals. We receive a good many requests from commercial firms to investigate some of these questions.

DR. HUGH L. DWYER (KANSAS CITY, Mo.)—In a paper delivered at the meeting of the Milk Commissions yesterday, allusion was made to the giving of egg yolk as a source of iron, and it was stated that fifteen yolks a day would be needed if they were the sole source of iron. We were advised to fortify milk by the addition of a mixture of iron, manganese and copper. Cereals were shown to have no effect. The paper was presented by a professor of agricultural chemistry at the University of Wisconsin.

DR. ABT—Have they patented the manganese?

DR. COOLEY—I am, as I have intimated, not at all sure of the desirability of the routine addition of iron to milk as a preventive of nutritional anemia. If one is to base one's ideas on Helen Mackay's work, one must remember that she seems to have been dealing with a rather inferior group of children and that the 'normal' hemoglobin curve which she obtained by adding iron to the milk was no better than observers in other parts of the world have observed when no special feeding was given.

If iron, iron and copper or iron and liver were surely a preventive of the common anemia of premature and twins I should think it worth using. Dr. Abt is one of those who have helped to prove that this anemia is not readily prevented in this way. I believe that this particular anemia is probably due to underdevelopment of the hemopoietic system, in which one would hardly look for much help from drugs. This is a different thing from the anemia due to iron reserve exhaustion which comes later in the first year and also to which premature infants and twins are peculiarly susceptible. I believe that proper feeding of the child should take care of this.

DR. DWYER—What is egg yolk good for?

DR. COOLEY—It is an excellent food and contains lipids and some vitamins. There is a real use for vitamins in the treatment of some anemias. While there is no particular type of anemia that can be definitely associated with any avitaminoses, children who are so poorly fed as to develop an avitaminosis are likely to have anemia also. If you take care of the vitamin lack, you will help in the cure of the anemia.

DR. BERNARD BERNBAUM (DETROIT)—Do you agree with Isaacs about the use of vegetables? 'Why irritate your patients with spinach when you can give them iron?'

DR. COOLEY—I don't think that the question of the use of vegetables has yet been satisfactorily explored. I should not give them just because of their iron content. They are however, a part of the good general diet which everyone thinks should be a part of the general regime in any anemia, especially those of the nutritional type.

DR. PRESTON McLENDON (WASHINGTON, D. C.)—What hemoglobin level do you advise for iron administration?

DR. COOLEY—That depends on the cause of the anemia, whether it has developed slowly or rapidly. In some anemic states you may have a pretty low

hemoglobin level and get prompt recovery without any special iron treatment. The crises of hemolytic icterus sometimes offer good examples of this. In nutritional anemia, or any "iron deficiency" anemia, I think I should give iron if the hemoglobin were 10 gm or less, because I like to see the children recover rapidly.

DR ABT—I have always followed Czerny's teaching. In 1912, I think, he showed that in those alimentary anemias caused apparently by the exclusive and excessive feeding of milk the patients did better if milk was practically eliminated from the diet.

DR COOLEY—Czerny and Glanzmann believed that milk had a definitely deleterious effect in these anemias, which they tried to ascribe to a hemolytic action of the fatty acids. Their work was not, to my mind, very convincing. The idea had a considerable following for some years but has largely been abandoned. You may have read Baar's monograph on the subject. He did just the opposite to the teaching of the Czerny school, he treated the "milk anemias" by giving more milk instead of less and claimed as good results, or better. There is, of course, thus much to it—if a child gets too much milk, it will interfere with his taking the good general diet that we think he ought to have. I have never believed that "milk anemia" was an indication for the elimination of milk.

DR ABT—Not for elimination, but for cutting down.

DR COOLEY—We cut it down to encourage the taking of other things. One of the best things you can give in these cases is meat, which is probably worth more than the vegetables.

QUESTION—What therapeutic value has ventriculin?

DR COOLEY—We have never used it. It has seemed to me that it was brought out to meet a specific indication in pernicious anemia and perhaps in some other achlorhydric anemias of adults and that there are few if any comparable anemias of childhood in which one would expect it to be useful.

We have seen recently what we believed to be a queer response to ventriculin. A child, whose real trouble was hemolytic icterus, was brought to us after prolonged treatment with ventriculin. He had achylia gastrica, pronounced macrocytosis with high color index, and a very high reticulocyte count. The picture might almost have been that of a pernicious anemia in a remission, except for the fact that pernicious anemia does not occur at that age. We stopped all treatment, and in a comparatively short time the macrocytes, which were the queer thing in the picture, had disappeared and been replaced by microcytes. We thought that ventriculin had probably stimulated the macrocyte response.

DR GEORGE J FELDSTEIN (PITTSBURGH, PA)—I have been told by men from southern regions that they see anemia resulting from excessive exposure to the sun. Have you seen anything of this? I suppose that dysentery or parasitic infestation might be a factor. Have you found parasitic infestation a common cause of anemia?

DR COOLEY—We have so few cases of parasitic infestation that my knowledge of the anemia they cause comes chiefly from the literature. I have seen a whole family with serious and prolonged anemia due to hookworm. There seem to be two types of anemia caused by quite a variety of parasites. Some, like the hookworm, actually draw blood, causing an anemia of the type due to chronic bleeding. An other type is generally explained as due to toxins produced by the parasites. A few cases of the pernicious anemia caused by the fishworm have been reported in children, but these cases are rare.

I have no knowledge of anemia caused by the sun's rays, but remembering the marked effects of sunlight on certain types of blonds, I should consider it not impossible.

QUESTION—What can we say to the otolaryngologists who are always harping on the blood in relation to the chronic running ear we get at this season?

DR. COOLEY—I think you might say that, if they will cure the ears, you will cure the anemia. There is no doubt about the vicious circle in the alimentary infectious anemias. The anemia makes the infection worse by lowering resistance. The infection aggravates the anemia. In the more troublesome ones there often seems to be a constitutional susceptibility. It is a difficult chain to break. This is one of the conditions in which I think there is often indication for repeated transfusion.

DR. PHILLIP S. ASTORWE (KANSAS CITY, Mo.)—I think that our ideas as to the life of the red cell after transfusion have changed considerably in the last five or six years. Ahlby, some fifteen years ago studying cells transfused from the so-called universal donor showed that the life of the cell is about sixty days. More recently Lonstetter and Lovine in describing two new blood groups, showed by agglutinin tests that the transfused cells were still in circulation after fifty to seventy days. Another method of studying this is by volume determinations. After transfusion both plasma volume and cell volume are increased. The increase in plasma volume lasts only about forty-eight hours, while the cell volume remains up for four or five weeks, and the hemoglobin volume is increased for nearly as long a time. From these several methods I think we can conclude that the life of the transfused cell is longer than we have been in the habit of thinking.

DR. COOLEY—I think it is evident that, since the transfused cells must be of very different ages when they are put into the recipient's circulation, they will degenerate and break up after varying times. In the case of which I spoke in which there seemed to be no hemolysis of the transfused cells, we found that we had to repeat the transfusion on the average every three weeks or less. This did not of course show that some of the cells might not have a considerably longer life.

DR. ABRAHAM B. SCHWARTZ (MILWAUKEE, WIS.)—Have you seen anything in children comparable to what has been reported in adults concerning the relation of the use of amidopyrine to agranulocytosis?

DR. COOLEY—I have not. There are very few cases of malignant neutropenia reported as occurring in childhood, and some of these have been doubtful. After all, there are not many children to whom one would give this drug and the proportion of adult users of it who develop the neutropenia is small.

DR. WALLACE B. TAGGART (DAYTON, OHIO)—Do you feel that some children respond to infections with a lymphocytosis where you would expect a leucocytosis?

DR. COOLEY—A lymphocytic response to pyogenic infection?

DR. TAGGART—Pneumonic infection.

DR. COOLEY—I should say that must be a rare experience. In some very severe infections you may see a relative lymphocytosis, but that is due to pronounced marrow hypoplasia or aplasia. Cell responses do vary of course. Occasionally one sees a pronounced eosinophile increase instead of the ordinary neutrophils response, so that the eosinophiles seem to replace the neutrophils but a replacement of granular cells by lymphocytes would hardly be expected.

DR. TAGGART—I asked the question because in the case I have in mind there was in the early stage some doubt as to differentiation between an infectious proc-

ess and leucemia. After the first count of 17,000 with 85 or 90 per cent lymphocytes, the patient developed bronchopneumonia and the total count doubled, but the differential remained the same

DR. COOLEY—I can remember no experience like that

DR GERARD N KROST (CHICAGO)—Have you met with cases of leucemia which went through an aleucemic stage without any evidence of leucemia? I had a patient with a count of about 1,200, with 70 per cent lymphocytes and a high grade anemia, she lived about eight weeks. For the first six weeks of that time we gave her transfusions, there was rapid blood destruction, but all the lymphocytes were of the mature type. About a week before her death the count went up to 15,000, and practically all the lymphocytes were immature. The platelets, usually reduced in leucemia, were normal until a week or so preceding death, when they dropped rapidly, the spleen became enlarged for the first time, there was slight general adenopathy, and she died with purpuric manifestations. Unfortunately no postmortem was permitted. The final picture apparently was one of leucemia, though for about seven weeks of her illness it had been more like that of infectious anemia with agranulocytosis.

DR COOLEY—I think that is one of the most difficult diagnostic problems we have to meet, the question whether a condition like that, when first seen, is a leucemia or an aplastic anemia. I do not think that one can often make a positive diagnosis in the early stages. Most of them prove to be leucemias. We have recently been observing a case in which we changed our diagnosis between leucemia and aplastic anemia about once a week. It proved to be an aplastic anemia. The platelets are usually reduced in leucemia, but I have seen one or two in which they were not down to what I should consider the bleeding level, though there were purpuric symptoms.

DR HARRY M GREENWALD (BROOKLYN, N Y)—You can often get a better idea of the condition by study of the marrow.

DR. COOLEY—The leucemic infiltrations are not universally distributed throughout the bones, and in the early stages there may be parts of the marrow that are active for a considerable time. There may be in the course of a leucemia an occasional period of regeneration in which the blood comes back nearly to normal. It seems to me that such a condition is the probable explanation of periods in which the platelets are well up.

DR GREENWALD—Some time ago I had occasion to study the marrow in a case of aplastic anemia. From this study and from observations on agranulocytosis I am convinced that in these conditions there must be a constitutional inferiority of the marrow. You are probably familiar with the reports of malignant neutropenia following the use of phenobarbital. I don't think that will occur in a normal individual who has no predisposing peculiarity of the marrow. I gave fairly large doses of pyramidon to a group of children every three days and made careful blood studies. In not a single case were we able to find changes in the total count or types of white cells. We might go on with studies for a long time until we struck a child with a constitutional susceptibility to the drug.

You mentioned the effect of bone marrow. We have been interested to see that in aplastic anemia even though the patient eventually dies the disease seems to be arrested for a time by marrow administration.

DR COOLEY—We have seen a temporary effect such as you speak of. The fact seems to be, as I think you pointed out in one of your articles, that in a real aplasia the marrow is not capable of a permanent reaction. In the cases that result from poisoning by x ray, benzol, etc., I think that there is a possibility of recovery if the destruction has not gone too far because we have a cause which can be

completely removed. In the primary idiopathic form and in most of the secondary states I think we cannot look for recovery.

The matter of constitutional inferiority—diathesis, if you like that word—is one of the most important questions we meet in the whole subject of the anemias. When this is not a factor, it is not difficult to treat most of the anemias. In malignant neutropenia I think that the evidence for a predisposition is very striking. Some of the men are trying to explain it on the basis of an allergic hypersensitiveness to these particular drugs. This is at least plausible.

DR. THURMAN B. GIVAN (BROOKLYN)—Within the last three months we have had in our hospital an Italian boy with no apparent trace of negro blood, with sickle-cell anemia. His mother also had sickle cells. We removed his spleen and about six weeks later he died of pneumonia. I thought it might be of interest to add this to those cases already reported.

DR. COOLEY—They are always of interest. I counted recently fourteen cases, of which I had knowledge, of sickle-cell anemia in white children. Most, but not all, have been in Italian or Greek children. Cooke, of St. Louis, recently had two in what might be called an ordinary American family with no Mediterranean ancestry. I have no doubt that there are many more of these cases in white children. They are missed because the examination of the moist blood film has so largely gone out of fashion. If this were a part of our ordinary routine we should be saved some embarrassing experiences, like a recent one in our own hospital, when an Italian boy in an abdominal crisis of sickle-cell anemia was operated upon for appendicitis.

PROF. ARVID WALLGREN (GÖTEBORO SWEDEN)—Can you tell me whether sickle-cell anemia occurs in Italy and Greece?

DR. COOLEY—We have seen two patients from the Peloponnese, but so far as I know none have been reported by Greek physicians. The father of our patients told us that in the region from which they came the people went to herb doctors, almost never to real physicians. I suspect that the same condition obtains in Sicily and Calabria, from which districts our Italian patients seem to come. I know of only one report from Italy, and the illustration of the cells in that was not very convincing.

DR. ROBERT A. STRONG (NEW ORLEANS, LA.)—Are we justified in considering that erythroblastic anemia is confined to the Mediterranean races? Of the reported cases, one was in an English child and another in a negro.

DR. COOLEY—Those were our cases, and we found on further study that our diagnoses had been wrong. The mulatto (not negro) proved to have hemolytic icterus, and the English child was finally decided to have a secondary hemolytic icterus due to syphilis. All the others have been of Greek-Italian, and, I think, some of Spanish blood. Some reports from South America sound to me like erythroblastic anemia. I am not, however, a great believer in any strict racial limitation of disease. It seems to me to be rather a matter of geographic conditions. Erythroblastic anemia, sickle-cell anemia, and hemolytic icterus are all characterized by prevalence in certain districts and among certain peoples. Hemolytic icterus is now spread pretty well all over the world but it is found more often in people of German descent and is more prevalent in certain districts of Germany than anywhere else. Possibly it got its start in some segregated part of Germany. Some similar situation may account for the apparent limitation of sickle-cell anemia and erythroblastic anemia. It is interesting, however, to note that the literature seems to indicate a greater prevalence of splenohepatic diseases of all kinds in the Mediterranean races.

DR. STRONG—I have noticed that there have been some rather indefinite reports of bone changes in hemolytic icterus similar to those seen in erythroblastic anemia. Are they of the same type?

DR. COOLEY—We have seen these same rather vague reports of thick skulls and "tower skulls" and have been on the lookout for something of the kind, but we have failed to find it. Gansslen mentions something of the kind, but he describes also various physical peculiarities and malformations which I do not believe to be long to hemolytic icterus per se. I have suspected (with no definite reason) that his large series came from an isolated community in which there was a good deal of intermarriage with probability of other reasons for developmental abnormalities. Hemolytic icterus is, however, characterized by marrow hyperplasia, which might at times reach the point of causing the radiographic appearances, just as they do occasionally appear in sickle cell anemia.

DR. STRONG—What has been the average length of life after splenectomy in erythroblastic anemia?

DR. COOLEY—I cannot answer that question definitely. Only three patients are now living out of our series from whom the spleens have been removed. One, about ten years old, will probably die within the year. We are keeping her alive by a transfusion every two or three months. The second, about eight years old, is getting along very comfortably and may live for some years. Her younger sister, now about three years old, is subject to severe respiratory infections, in which she goes down hill fast and comes back slowly. One of them may carry her off at any time. In general, the duration of life in these patients seems to depend on the kind of infections they run into. They do not usually die of the anemia, but their resistance is poor. Most of them do not live past the tenth year, though one, originally reported by Stillman in 1927 as von Jaksch's disease, who had an early splenectomy, is still living at the age of twenty-seven years. This is the only arrested case of which I know.

DR. STRONG—I asked because we have a case under observation at the present time, reported from my department by Williamson a short time ago. The spleen was removed at twelve months. The child is now nine years old. The skin shows a copper-bronze Mongolian color, without discoloration of the sclerae, and I cannot see that this has changed at all. The bone changes, however, seem to me even more exaggerated than when the article was published nine months ago. We have been wondering how long we might expect to keep her alive.

DR. GREENWALD—Do you feel that the Mongoloid appearance of the patients is characteristic of this disease? Don't you find it in aplastic anemia?

DR. COOLEY—I should not expect it in aplastic anemia because I think that it is due to marrow hyperplasia. When the malar eminences are involved, there is the effect of high cheek bones. So far as the color is concerned, that may be seen in many anemias, but it is only in the conditions with pronounced marrow hyperplasia that we see the thick skull and the high cheek bones.

I think we have laid too much emphasis on this feature because it is so interesting when it is present. It may occur in sickle cell anemia, which is another disease with marrow hyperplasia. The negro traditionally has a hard skull and rather tough bones in general. It is true that in sickle cell anemia we do not see the general widening of bone and increase in marrow cavity present in the white child with erythroblastic anemia, but the skull changes do occur in moderate degree.

DR. CHARLES W. MARTIN (FAR ROCKAWAY, N. Y.)—I should like to know what rôle you think splenectomy plays in the treatment of some of the grave anemias.

DR. COOLEY—I touched on that in my preliminary discussion. In hemolytic icterus, hemorrhagic purpura and, we think, erythroblastosis of the newborn, the spleen is apparently directly concerned in the destruction of blood cells though we do not clearly understand the mechanism of the process. Since this, unlike other splenic functions, is not taken over by other depots of histiocytic tissue after splenectomy, in these conditions the operation usually effects a cure. Since in sickle-cell anemia, erythroblastic anemia, and the secondary hemolytic anemias, the cell destruction seems not to be directly due to splenic activity, the operation has little effect on the disease process. It is worth while to remove the organ sometimes in erythroblastic anemia and in some of the other diseases in which it becomes very large, simply to free the child of the burden of its weight. In 'splenic anemia' often looked on as the first stage of Banti's syndrome splenectomy is frequently advised as a possible preventive of the later development of bleeding and cirrhosis. In the related condition in which splenomegaly and gastric hemorrhage are early symptoms, splenectomy has proved very effective. Both of these disorders seem to depend on vascular changes originating in the spleen, and the operation is supposed to check their further development. It does not always have this effect, however. I mentioned earlier some theoretic possibilities in other disorders.

DR. HENRY F. HELMHOLTZ (ROCHESTER, MINN.)—Is the first stage of Banti's disease any easier to recognize than the later stages? How often do you make a diagnosis of Banti's disease?

DR. COOLEY—That is certainly a rare diagnosis in childhood. Splenic anemia is the wastebasket diagnosis in the anemias of childhood. As nearly as I can state the situation, if you have a condition with splenomegaly, anemia and leucopenia which persists, and you can rule out all the other things which might cause it (of which I can think of quite a number), you may conclude that this is perhaps the type of splenic anemia which later will develop into the Banti syndrome. If you remove the spleen, you will probably do no harm, and you may prevent the later symptoms. Our only cases of the Banti syndrome have followed splenectomy.

Splenectomy sometimes fails in cases where one would have expected success. One possible reason is the development of accessory spleens overlooked at the time of operation. Another is that while usually other parts of the reticuloendothelium do not take over the pernicious activity of the spleen occasionally they seem to do this, and after a time the symptoms recur.

DR. GREENWALD—I think one must warn the patient that splenectomy is not always a permanent cure for hemolytic icterus. In Berlin, I saw a patient who had had a splenectomy for hemolytic icterus and who was presented showing marked improvement. In 1928 I saw the same patient again with a marked recurrence, and practically the same as in 1921 before the splenectomy.

As to Banti's disease—I had occasion to observe a child who had a large spleen and severe hemorrhage. After the hemorrhage the spleen diminished and subsequently increased. Splenectomy was performed and so far the child has done well. Warthin and others believe that splenic thrombosis is the first stage of Banti's disease. The idea is that if you operate before the portal vein is involved, you may be able to effect a cure. Wallgren reported a series of patients with thrombosis of the splenic vein whom he had followed for a number of years and who remained well. On the other hand, he says that these children sit on a volcano.

DR. COOLEY—We have not, in our few operations for this type of disorder, been able to demonstrate thrombosis in the splenic vessels at the time of operation or in the excised spleen nor has this been a uniform finding in reported cases. It

would simplify matters if we could be satisfied to put this whole rather vague group under the heading of thrombosis of the splenic vein.

DR. JOHN F. SINCLAIR (PHILADELPHIA)—What has been your experience with the use of destructive x rays on the spleen instead of splenectomy? We had a child of two months with thrombocytopenic purpura, and, being unwilling because of its age to subject it to splenectomy, we spent several months with transfusion, and ultraviolet rays. Finally, knowing that Pancoast had treated several older children with the deep x ray, we persuaded him to undertake the treatment of this child. After eight treatments his symptoms disappeared, and during the six years' observation since then, his platelets have remained up and he has had no recurrence. He has never, however, recovered the retractile clot.

DR. COOLEY—There are two possible substitutes for splenectomy. One is the deep x ray, and the other, ligation of the splenic artery, both of which have been successfully used. I have had little experience with the x ray treatment. The objection to it is that it is slow. In a case such as yours, in which there is an objection to splenectomy, or in a mild chronic case I think there may be a good indication for its use, in the ordinary case it has seemed to me that splenectomy was preferable. Ligation of the artery might be a useful procedure in case troublesome conditions were met with at the time of operation which would prolong the operation and increase the risk of shock, but under ordinary conditions, once the abdomen has been opened, it would seem to me to be better to take the spleen out.

DR. GREENWALD—Thrombocytopenic purpura means splenectomy, undoubtedly, in most cases, but there are cases in which it does not stop the bleeding and others in which it is contraindicated. In such cases I should recommend snake venom. I shall report shortly a group of patients benefited definitely by intracutaneous injection of diluted venom. The platelet counts were increased, and retraction of the clot returned. Bleeding ceased in all but one case, in which there was recurrence after several months.

DR. COOLEY—Would you think it advisable to try the venom always before resorting to splenectomy? I hesitate to recommend splenectomy when I first see a patient with purpura as, on the one hand, so many of them recover without operation and, on the other hand, the operation is not always successful, though we have had no failures. I suppose that it would be wise always to ascertain by marrow puncture the state of the megakaryocytes before going ahead with splenectomy.

DR. GREENWALD—A trial of the snake venom is harmless. If it fails, you can still resort to splenectomy. I recommended in an article in THE JOURNAL OF PEDIATRICS that marrow puncture should be performed in every case of thrombocytopenic purpura to see if there are megakaryocytes present. If they are, splenectomy is likely to be of benefit.

DR. STRONG—What type of venom is used?

DR. GREENWALD—Moccasin venom, diluted 1:3,000. It decreases the vascular permeability, which is the chief reason for the bleeding in purpura.

DR. STRONG—Moccasin venom is hemotoxic. Might it not cause hemolysis?

DR. GREENWALD—It does not. Possibly it would if given undiluted, but in this dilution the doses are very minute.

DR. ASTOWE—How soon does the bleeding stop?

DR. GREENWALD—In one case of severe hematuria, the bleeding stopped after five days. In a child with a severe epistaxis and extensive subcutaneous effusions, bleeding stopped after forty eight hours.

DR. ASTROWE—Does the platelet count come back?

DR. GREENWALD—It improved in every case, not to the normal count, but to 150,000 or 200 000. In one case it went to normal and dropped back.

DR. ASTROWE.—Do you find bleeding closely related to the platelet count?

DR. GREENWALD—I have seen a count of 80 000 with no bleeding and bleeding with a count of 100 000.

DR. COOLEY—You may have a patient in whose blood you can find only an occasional platelet and who still does not bleed. I have seen only one who bled with as many as 100 000 platelets. Nobody understands the mechanism of the capillary permeability but there is no question as to its importance in determining the purpura bleeding.

QUESTION—Is the effect of the venom more lasting than that of the anti venom?

DR. GREENWALD—I cannot say. I have read the article to which you refer reporting the cure of a soldier by the use of antivenom after failure of all other measures to stop extensive bleeding. We tried the antivenom in a severe case of purpura after that report, but it was not successful. We cured the patient by repeated transfusion.

DR. COOLEY—It is difficult to estimate the value of any method of treatment of purpura because there is so often spontaneous cessation of bleeding and single cases do not prove much.

DR. ELEANOR LESLIE (Chicago)—The inconsistency between platelet counts and coagulation time is often due to the fact that the platelets have been broken down by admixture with tissue fluid or contact with glass. In such cases one may find a low platelet count and a short coagulation time. The rapidity with which tissue fluid breaks down platelets often leads to an inaccurate estimation of platelets when the blood is obtained through a puncture wound.

DR. COOLEY—Mills, of Cincinnati who has written a good deal about the clotting function, thinks that you get a better picture of what goes on in case of bleeding if you take blood for examination from a finger prick; in other words, if you have tissue fluid mixed with it. I think most of us believe that venous blood is better. One must be careful, in making the venipuncture, not to draw any tissue juice into the needle.

DR. LESLIE.—In order to avoid the breaking down of platelets by tissue fluid or contact with glass, I have been taking blood for platelet counts by venipuncture receiving the blood into an ice-cold oiled syringe and introducing it immediately into paraffined tubes imbedded in ice. The platelet count is made from the plasma after the cells have settled out, and the coagulation time of the plasma is determined in paraffined tubes. If there has been difficulty in obtaining the blood, or if there has been an admixture of cerebrospinal fluid as may happen when the blood is taken from the superior longitudinal sinus, we find low platelet counts and short coagulation times. If there is no admixture of tissue fluid or cerebrospinal fluid the platelet count is high—in newborns 500 000 to 700 000—and the coagulation time at 25° C. in paraffined tubes, 10 to 20 minutes. Further centrifuging of this plasma in paraffined tubes in ice, yields an upper layer of platelet-free plasma which may have a coagulation time of several hours.

DR. COOLEY—I have an impression that the whole question of the hemorrhagic disorders and their relation to the clotting mechanism will bear a good deal more study.

ROUTINE MEASURES FOR THE PROPHYLAXIS OF COMMUNICABLE DISEASES

REPORT OF SPECIAL COMMITTEE ON PROPHYLACTIC PROCEDURES AGAINST COMMUNICABLE DISEASES

A YEAR ago a committee was appointed from the Academy of Pediatrics to recommend approved procedures for the prophylaxis of the communicable diseases of childhood. The following report duplicates a certain amount of previous effort, but an attempt has been made briefly and explicitly to present directions for the performance of those immunization procedures which are of practical value and necessity. It is unavoidable that a certain amount of personal opinion should enter in selection of procedures and direction for their performance, but in controversial matters we have attempted to follow generally accepted practice in this country without entering into argumentative discussion. The report is offered simply as an outline for the guidance of pediatricians and general practitioners with the hope that it may prove useful. It is not unlikely that certain modifications may be necessary to suit varying conditions and modifications will of course be necessitated by advances in knowledge. Dr J E Gordon, Detroit, Dr John A Toomey, Cleveland, Dr E B Shaw, chairman, San Francisco, compose the committee.

DIPHTHERIA

Age—Immunization should be routine at one year. It is a desirable practice for the physician to send an appropriate notice at the child's first birthday. Prophylaxis may be performed to advantage between the sixth and eighteenth month and should be advocated up to ten years. Nonimmune adults should be protected if they are unusually exposed to infection, as in the cases of medical students, dentists, nurses, social workers, school teachers, public health workers, and others with occupational hazards.

Material—Toxoid should be employed for young children. They seldom manifest other than local reactions. Since adults and children more than ten years of age frequently have unpleasantly severe reactions, it is advisable in this age group to employ toxoid in doses initially smaller than those used for younger children. It is permissible to substitute toxin antitoxin in the older age group. Toxoid should never be injected unless the solution is perfectly clear.

Dosage—Toxoid for infants and children under ten years. Two injections are given at least two weeks apart. It is permissible to lengthen this interval slightly. The first dose is 0.5 c.c., the second, 1.0 c.c. Injections are made subcutaneously in the arm.

The dose of toxoid for persons over ten years. The immunization procedure should be individualized, depending upon the reaction produced by an initial small dose of toxoid. The first dose should be 0.2 c.c. In most instances this amount produces no marked reaction and can be followed at intervals of two weeks by a second dose, 0.5 c.c., and thereafter in two weeks by a third, 1.0 c.c. In the event of a reaction after the first small dose the amounts subsequently injected should be cautiously increased, or the same dose repeated. Immunity may be produced by three injections as small as 0.2 c.c. each.

Toxoid is the preferred immunizing agent for persons of all ages, but toxin antitoxin mixture, which produces generally less severe reaction in older individuals, may be used in the older age group although it does not produce immunity with as much

certainly as toxoid. Three successive injections of toxin antitoxin mixture in amounts of 1 c.c. each should be given from one to two weeks apart.

New immunizing agents are being introduced, which may be desirable to employ when their usefulness has been fully demonstrated. Alum precipitated toxoid is prominent among these. It has the advantage of requiring only a single dose because of the slow rate of absorption. This preparation is used in amounts of 0.5 c.c. to 1.0 c.c. (varying with different preparations) and should be administered by deep subcutaneous injection into the arm.

Indications for Schick Test—(1) A Schick test preliminary to immunization is unnecessary for children aged less than seven years. For older persons it is desirable to determine the need for immunization by this means. (2) Those who have received diphtheria prevention should be tested six months later for their Schick reactions. This determines the presence or absence of immunity. If the reaction is positive, injections of the immunizing mixture should be repeated. Often a single additional dose will be sufficient.

Schick Test Material.—Diphtheria toxin for Schick tests is supplied in two forms. (1) Undiluted toxin is contained in a small vial, together with a second vial of normal salt solution for diluting the toxin. Dilutions are to be made immediately before the material is used. Diluted toxin is not to be relied upon after one day. (2) Schick test toxin in peptone diluted ready for use can be obtained commercially and is stable for a period of months. This material is particularly useful when only one or two children are to be tested. Experience indicates that it is as reliable as freshly diluted material, and its use is recommended.

Technic of Schick Test.—To perform a Schick test inject intracutaneously 0.1 c.c. of the diluted toxin (representing 1/50 m.l.d. of toxin) into the flexor surface of the forearm at the junction of the upper and middle thirds. A superficial bleb should result.

Reading the Schick Test.—The result of the Schick test should be determined at the end of seventy-two hours. There are then two possibilities—no reaction or a positive reaction. A positive reaction consists of redness, possibly with induration 1 cm. in diameter or larger; this signifies lack of immunity. If the test is negative, it should be read again on the seventh day. Desquamation and pigmentation often follow the positive reaction.

Schick Test Control.—A control test may be performed on the opposite arm if desired. Similarly diluted toxin, heated to 80° C. for ten minutes, is used for this purpose. Practically a control test is unnecessary especially in younger age groups where pseudoreactions seldom occur.

Prophylactic Use of Diphtheria Antitoxin.—This is seldom advisable. When the contacts are not to be seen subsequently or are not under close observation, 1,000 units of diphtheria antitoxin may be injected intramuscularly into the lateral muscles of the thigh halfway between the hip and the knee. By preference the contacts should be separated from the patient, their susceptibility determined by Schick tests and cultures made of the nose and throat for diphtheria bacilli.

Precautions.—When horse serum is to be administered, especially for prophylaxis of disease, the patient should be investigated carefully for evidence of hypersensitivity to horse serum. Previous injections of horse serum including toxin antitoxin mixtures are significant. Known sensitiveness to horse emanations—horse asthma—is important. The patient may be tested for serum hypersensitivity by the injection intracutaneously of 0.1 c.c. of a 1:10 or 1:100 dilution of the antitoxin. The appearance within five to thirty minutes of a wheal or a marked zone of erythema about the site of injection is an indication for care in the administration of the full dose. With evident serum hypersensitivity, a prophylactic dose of anti-

toxin should be given in divided amounts beginning with 1 c.c. of a 1:100 dilution in saline solution. At intervals of thirty to forty minutes increasing amounts of serum may be given until the full dose is completed. Horse serum is best given into an extremity, in such a location that rapid absorption can be impeded, if an immediate reaction ensues, through application of a tourniquet proximal to the site of injection. Epinephrine solution of 1:1,000 should be kept in readiness for combating reactions.

SCARLET FEVER

Active Immunization—Active immunization through injection of increasing doses of scarlet fever streptococcus toxin weekly for five weeks has been proposed as a preventive measure. It is of value in nursing groups, for the personnel of communicable disease hospitals, in orphanages, and for others intimately and constantly exposed to scarlet fever. It is not recommended as a general public health procedure, since reactions both local and general are frequent, are often severe in adults, and are not altogether absent in children, and for the reason that the degree and duration of immunity have not been definitely established. A number of physicians, however, use it in their private practice.

Tests for Susceptibility—A test for scarlet fever susceptibility is made by injecting intracutaneously 0.1 c.c. of scarlet fever toxin (supplied by commercial houses for this purpose). This is called the Dick test. Although it is fairly accurate, it must be pointed out that it is not perfectly reliable, persons with negative Dick tests have been known to contract scarlet fever. Tests should be read in twenty-four hours, a positive reaction (lack of immunity) consists of an area of redness or induration at least 1 cm. in diameter.

Convalescent Scarlet Fever Serum.—Convalescent scarlet fever serum in 10 c.c. amounts has been advocated as of value in passive protection. The evidence is inadequate for a definite opinion.

Scarlet Fever Antitoxin—Scarlet fever antitoxin has been recommended for passive protection against scarlet fever. Its use is frequently accompanied by unpleasant horse serum reactions, and the evidence regarding its value is inadequate for a definite opinion.

TYPHOID FEVER

Typhoid immunization is not to be recommended for universal application. Its use should be restricted to those whose duties bring them in active contact with the infection, such as doctors and nurses, those who travel in regions where the incidence of typhoid is great, and more particularly those whose vacations are spent in regions where the water supply is questionable or the risk of acquiring typhoid is appreciable. In southern rural communities general programs of immunization against typhoid fever have been used to good advantage.

Vaccine—The usual vaccine is designed to protect against typhoid, paratyphoid A, and paratyphoid B. Injections should be given at intervals of one week. The first dose is 0.5 c.c., the second and third dose, 1 c.c. each. Injections may be given from five to fourteen days apart, but a reaction from the previous injection should have disappeared before administering the next.

Duration of Immunity—Immunity after typhoid immunization lasts at least two years. Typhoid immunity cannot be determined by any laboratory test. If protection is to be assured beyond that time, a second course of injections should be given. Where continued protection is essential, one dose may be given each year following the original course of three.

WHOOPIING COUGH

Vaccine.—If any good is to be derived from the use of vaccines, they should be prepared from freshly isolated strains and should be given in sufficiently large doses to provoke fever.

Indications.—Prophylactic immunisation is commonly employed in the case of those who have been exposed to the disease. Its beneficial effects are uncertain. Vaccines ordinarily contain five to ten billion killed organisms per centimeter. Successive doses of 0.25, 0.5, 1.0, and 1.5 c.c. are given at intervals of two to three days. The same vaccine is used with uncertain success after the development of the disease.

Sauer has recently recommended routine immunisation of children against whooping cough, comparable to the program for diphtheria prevention, and advocates large doses of freshly prepared vaccine prepared from organisms grown on human blood medium.

Convalescent Serum.—Convalescent serum from patients recovered from whooping cough has been used by a few physicians in amounts of 10 c.c. for children known to have been exposed to the disease. The evidence in favor of this procedure is indefinite.

MEASLES

There is no method for active protection against measles. The disease may be prevented, or better modified by the injection of the blood serum of a person recently convalescent from the disease or by the injection of the blood or blood serum of most adults.

Convalescent Serum.—Human blood serum taken one to three weeks after the fever of measles has subsided contains protective substances against the disease. When administered shortly after exposure in doses of 10 c.c. intramuscularly it may protect against the disease. It usually lessens its severity and is particularly recommended when exposure occurs during the course of another illness, especially respiratory infections. Under ordinary circumstances it is more desirable to produce modified measles than to protect completely. Ten cubic centimeters of serum given on the sixth day after exposure to a person in continuous contact (i.e., on the second day that the patient has the rash) produces partial protection. The contact usually develops measles in a mild form with little or no fever and an atypical rash. Convalescent serum given in ordinary amounts more than seven days after exposure is without much effect.

Adult Blood.—About 30 c.c. of normal whole blood or 20 c.c. of normal serum is said to produce an effect equivalent to that of 10 c.c. of convalescent serum. Measles modified by convalescent serum or normal blood apparently produces a permanent immunity comparable to that from an ordinary infection.

SMALLPOX

Vaccination.—During epidemics of smallpox, vaccination may be performed at any age. All children should be vaccinated between the sixth and twelfth month of age. This should be repeated whenever the disease is epidemic or in the presence of unusual likelihood of exposure, as in foreign travel.

Material.—Any glycerinated vaccine may be used. A record should be kept of the lot number of the vaccine.

Location.—Vaccination may be done on any skin surface usually the arm or the leg is used. The preferred site is the inner aspect of the arm at the junction of the lower and middle thirds.

Preparation—The site should be thoroughly washed with soap and water, scrubbed with 95 per cent alcohol and allowed to dry

Multiple Pressure Method—A drop of the virus is placed in the center of the cleansed area. Holding a small sterile needle parallel to the skin surface, the needle is quickly stroked against the skin through the drop of virus, about ten to fifteen strokes are sufficient. The excess of virus may be removed with sterile gauze.

Dressings—Tight constricting dressings or shields are to be *strictly* avoided. Two or three thicknesses of sterile gauze may be placed over the area and lightly fixed with adhesive tape, in such a way that constriction of the area is avoided. It is permissible to apply no dressing.

Kinds of Reaction—(a) In a successful primary vaccination, a pustule is present at the end of seven days, usually appearing about the fifth day. (b) An unsuccessful vaccination shows no reaction to the virus and confers no protection against smallpox. Those who fail to react after a primary vaccination with the production of a pustule should be promptly revaccinated. (c) Persons revaccinated after a previously successful result may show a reddened, inflamed macular or maculopapular area at the vaccination site at about forty eight hours, an immunity reaction. This is evidence of persistent immunity from the previous vaccination.

Successful vaccination wounds may be left alone except for protection against secondary infection. The application of mildly antiseptic solutions of gentian violet, mercurochrome, or merthiolate is useful for this purpose. A secondary infection of the pustule may be cleansed with ether and painted with a mild antiseptic dye. Healing is usually complete after two weeks.

Smallpox vaccination and diphtheria immunization should be done at about the same period of infancy and may be combined. It is convenient to vaccinate at the same visit at which the second dose of toxoid is given.

POLIOMYELITIS

The risk of acquiring the disease is statistically small. Convalescent serum and normal serum have been proposed for passive protection during epidemics. The value of this procedure has not been conclusively demonstrated.

EPIDEMIC MENINGITIS

No present method for active or passive protection.

MUMPS AND CHICKENPOX

Blood serum from recent convalescent individuals has been used for protection against these diseases. Their value is not unquestionably proved and is practically limited to institutions. Indications for such use are not frequent because of the mildness of these infections.

RABIES

Rabies prophylaxis is necessitated by the bite of a rabid animal and is advisable whenever there is a possibility that secretions of a rabid animal have been brought in contact with the abraded skin or mucous membrane. It is important that treatment be instituted at the earliest possible moment. Contaminated abrasions or bites should invariably be cauterized with fuming nitric acid. Other antiseptics have been less satisfactory. Prophylactic treatment should be most energetic following wounds in close proximity to the central nervous system, in those of an extensive nature, and in which treatment is delayed, less heroic measures are permissible with more distal and superficial lesions.

The original method of Pasteur is not now commonly used. Different preparations are supplied by various commercial houses, but they have the common property of being emulsified rabbit cord infected with *fixed* virus which has been killed (in some cases simply attenuated) by the use of chemicals or physical agents. All preparations share the common property of being incapable of producing rabies in the human being as a result of injection. The Semple preparation, a phenolized cord emulsion, is most commonly recommended. The Cumming and Harris methods are employed by some manufacturers.

The prophylactic treatment usually consists of fourteen daily injections of the dose recommended by the commercial house. Injections are given subcutaneously usually into alternating sides of the abdominal wall, but may be given elsewhere with equally good effect. In cases in which there is extensive injury or if the injury is in close proximity to the central nervous system or if there is more than usual suspicion of rabies twenty-one or twenty-eight injections should be employed. Sometimes it is recommended that injections be given twice daily if the nature of the case indicates urgent and intensive immunization.

TETANUS

Tetanus antitoxin should be used prophylactically in cases in which there is danger of contamination of a wound with horse manure or human excreta. It is particularly indicated in puncture wounds and wounds about the head.

The prophylactic dose is 1500 units injected subcutaneously. This may be repeated at intervals of five days if the danger of infection is particularly great. In using tetanus antitoxin as a prophylactic measure the same precautions should be observed as are recommended for diphtheria antitoxin.

PEDIATRIC DEPARTMENTS IN GENERAL HOSPITALS

(Continued)

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES, AMERICAN ACADEMY OF PEDIATRICS

REGIONS III and IV include the midwestern and far western states. In Region III, ten states report that one or more general hospitals have at least twenty four beds and bassinets for infants and children. These ten states are Colorado, Illinois, Indiana, Kansas, Michigan, Minnesota, Missouri, Nebraska, Ohio, and Wisconsin. In Region IV only California and Washington report pediatric departments in general hospitals of the above minimum number of beds.

Table I presents the distribution of the respective services by regions and by states and also reveals the relative size of the services.

Ten states are represented in Region III and two, in Region IV, there are sixty five hospitals in the former and fourteen in the latter region, representing a total bed capacity of 2,707 and 878, respectively, bassinets number 1,697 and 505 in the same order. The largest single service is found in California, one hospital there reporting 270 beds for children. Second and third largest services are found in Michigan and Ohio with 200 and 100 bed services respectively. The hospital having the greatest number of bassinets is again found in California, the largest service there having 120 bassinets, Michigan reports the next largest with 102 bassinets and Wisconsin is third with 75.

None of the hospitals in either region reports less than twenty beds for children. In Region III Ohio has twenty hospitals which report pediatric services of the size considered in this report, more than twice as many as found in any other state. California in Region IV reports twelve such services.

Residents—In Region III, fifteen hospitals employ twenty six pediatric residents. Only thirteen of these residents give their time exclusively to the pediatric department. In each instance the resident receives a salary. These salaries vary from \$20.00 to \$150.00 per month. In Region IV, ten hospitals employ fifteen residents among whom seven confine their activities exclusively to the pediatric department. The salaries in this instance vary from \$10.00 to \$125.00 per month.

Internes—In Region III, six hospitals are found to have a total of twelve internships in which the internes may devote their time exclusively to pediatrics. Region IV has six such internships in three different hospitals.

Attending Staff—In Region III among sixty five hospitals there are 295 pediatricians on the attending staffs. In Region IV, ninety six staff members are reported. The period of service varies from one to twelve months. Many services are reported of three or four months, but the majority seem to be for a twelve-month period.

Newborn Service—In Region III, thirty one hospitals, or about 50 per cent, maintain the newborn service under the supervision of the pediatric department. In Region IV, eight hospitals, or about the same percentage, maintain such services, all of them being in California.

Nursing—In Region III a head nurse is in charge of the pediatric department in all hospitals. These nurses have had special pediatric training in all but three instances. Again as has been found frequently in the reports on Regions I and II, these nurses in many instances have had only three or four months of special pediatric

TABLE I

STATE	NUMBER OF HOSPITALS	TOTAL BEDS	TOTAL BASSINETS	LARGEST NUMBER OF BEDS IN ONE HOSPITAL	SMALLEST NUMBER OF BEDS IN ONE HOSPITAL	LARGEST NUMBER OF BASSINETS IN ONE HOSPITAL	SMALLEST NUMBER OF BASSINETS IN ONE HOSPITAL
<i>Region III</i>							
Colorado	3	83	70	38	20	40	0
Illinois	8	247	159	47	23	60	3
Indiana	5	182	133	68	25	51	5
Kansas	3	124	61	52	32	20	16
Michigan	8	517	311	200	29	102	4
Minnesota	5	199	112	70	25	33	5
Missouri	5	203	100	70	24	06	12
Nebraska	3	77	40	28	21	20	6
Ohio	20	843	500	100	24	74	2
Wisconsin	5	232	100	80	33	75	10
Total	05	2707	1607				
<i>Region IV</i>							
California	12	807	404	270	27	180	16
Washington	2	71	101	70	35	31	50
Total	14	878	505				

training In Region IV all hospitals have a head nurse in charge of the pediatric department. In two instances these nurses have not had special pediatric training. However, it is in contrast to note that there are very few instances in which the head nurses have not had one year or more of special pediatric training.

Fifty eight hospitals in Region III have student nurses, the average service being from two to four months. These nurses may have from one to twenty five infants under their care, the average being about four to six in a children's department or from one to sixteen children (average of four to eight). In Region IV, thirteen hospitals have student nurses, and the relative number of nurses to care for the infants and children is about the same as in Region III.

Social Service—Twenty hospitals in Region III and five in Region IV maintain a special social service department for children.

Diet Kitchen—In Region III, fifty hospitals have a special diet kitchen for infants and twenty nine have one for children. In Region IV, ten have one for infants, and six have one for children.

Schooling—Twenty hospitals provide schooling for patients in Region III, and five provide it in Region IV.

Recreation—Thirty hospitals provide for recreation in Region III and six, in Region IV.

Dispensary—In Region III, forty hospitals maintain a dispensary for infants and children. Most of these clinics are open daily, and the attendances average from fifteen to thirty patients per day. The extremes in variation of attendance are as low as one and as high as forty seven per day. In Region IV, eleven hospitals maintain a dispensary for infants and children with attendance figures similar to those in Region III with extremes of as low as eighteen and as high as 125.

In Region III the same staff serves in both hospital and dispensary in thirty seven instances. The resident receives experience there in thirteen, and the interns, in thirty one instances. In Region IV these figures are ten, seven, and nine, respectively.

Table II presents figures concerning admissions, deaths, autopsies, and percentage of deaths and autopsies among the hospitals in Regions III and IV.

COMMENT

As might be expected in relatively denser areas of population, we find in Region III a fairly large number of hospitals with pediatric departments of twenty four or more beds. However, nearly one third of the total is found in one state, Ohio, and over 55 per cent among three of the ten states in that region. Specifically they are in Ohio, Michigan, and Illinois.

Hospitals which can be considered in this report are found in only two states of Region IV, California and Washington. Fourteen hospitals are reported from these two states, twelve, or over 85 per cent, of them are in California. However, these two states have available about one third as many beds and bassinets as reported for the ten states of Region III.

Only fifteen hospitals of the entire group in both regions employ pediatric residents. Although twenty six residents are reported, only half of this number give their time exclusively to the pediatric departments.

Only eighteen internships in which a man may spend his time exclusively in pediatrics for one year are reported, and these are available only in nine hospitals.

Little need be said here concerning attending staffs, except that, in common with previous reports on Regions I and II, we find too many instances in which services are only for one, two, three, or four months' duration. We wish again to emphasize, at the risk of boring, that to our mind this is too short a time if that service is to be efficiently conducted.

TABLE II

STATE	NUMBERS ADMITTED		DEATHS		AUTOPSIES		PERCENTAGE OF DEATHS		PERCENTAGE OF AUTOPSIES	
	NEWBORN	CHILDREN	NEWBORN	CHILDREN	NEWBORN	CHILDREN	NEWBORN	CHILDREN	NEWBORN	CHILDREN
<i>Region III</i>										
Colorado	1527	4033	106	88*	67	46	0.0	1.7	30.4	2.2
Illinois	3111	154	117	11	46	47	87	21	30.4	40.1
Indiana	1096	3300	100	183	81	29	50	54	15.8	15.8
Iowa	833	680	10	47	8	1	1.0	0.0	50.0	31.0
Michigan	5330	0100	192*	730	93	130	3.5	7.6	48.4	39.7
Minnesota	2196	301	04	141	54	90	4.3	4.6	57.4	83.8
Missouri	4360	4044	141	140	30	80	3.2	3.6	23.5	90.9
Nebraska	1350	1678	51	7	30	31	3.7	3.3	53.8	54.3
Ohio	10110	11784	445	606	210	288	4.2	5.5	47.1	43.8
Wisconsin	3494	4358	164	102	26	91	4.5	2.7	15.8	50.0
Total	31744	4002	1426	1002	588	833	4.1	4.2	37.7	43.7

Region IV

STATE	NUMBERS ADMITTED		DEATHS		AUTOPSIES		PERCENTAGE OF DEATHS		PERCENTAGE OF AUTOPSIES	
	NEWBORN	CHILDREN	NEWBORN	CHILDREN	NEWBORN	CHILDREN	NEWBORN	CHILDREN	NEWBORN	CHILDREN
California	7380	9711	27	687	90	180	3.0	7.0	30.0	7.0
Washington	1770	714	6	6	2	1	1	1	9	9
Total	9350	10425	33	693	92	181	3.1	7.1	39.0	7.0

As there are only two hospitals reported from Washington the failure of one to report figures as indicated above prevents accurate summary figures.

One hospital did not reply
Two hospitals did not reply

Only thirty nine, or about 50 per cent, of the hospitals in both regions maintain their newborn service under the supervision of the pediatric departments. Without wishing to seem impertinent, we suggest that these figures show considerable room for improvement. California has the best record of any state in the two regions in this respect with a figure of 75 per cent, Nebraska is next with 66 $\frac{2}{3}$ per cent.

Nursing care, as far as we can determine from the rather sparse information afforded by the questionnaire, is in most instances competent, although we again find too many head nurses who apparently have not had what we consider adequate pediatric training.

About 30 per cent of the hospitals in Region III and 40 per cent in Region IV mention a social service department for children. These are fairly good figures when one considers that many of the pediatric departments are small.

A large majority of hospitals in both regions maintain special diet kitchens for infants and many have one especially for children.

Less than 33 per cent in Region III and about 50 per cent in Region IV provide schooling for convalescents, while recreation is provided among about 50 per cent of hospitals in both regions. These latter figures again reveal that these two activities probably do not receive enough emphasis in many hospitals. Of course, in the smaller departments there are probably relatively few patients whose stay in the hospital is to be long.

Newborn mortality rates vary considerably for the various hospitals and states. In some hospitals the mortality rate is extremely low and probably reflects excellent obstetric and pediatric care, while among other institutions it is lamentably high. By state as well, there is quite a variation in these figures as evidenced by Nebraska with the low figure of 1.9 per cent and Colorado with a high one of 6.9 per cent. The total average of all states is 4.1 per cent, which is too high.

Alertness of medical thought and efficiency of medical procedure in hospitals is often reflected rather accurately by necropsy figures. Again we find a wide variation in our figures from a low of 8.0 and 15.8 per cent among infants and children, respectively, in Indiana to a high of 58.8 per cent for Nebraska among children and 63.8 per cent for Minnesota among infants.

This is the third report in an attempt to obtain much needed information concerning pediatric care in general hospitals of this country. In previous reports hospitals in Regions I and II of the American Academy of Pediatrics have been considered. A final report will be made in which the committee will attempt to coordinate the three previous reports and from that information to give concrete suggestions as to what should be done to improve pediatric care in general among the hospitals included in the report.

Academy News

The fifth annual meeting of the American Academy of Pediatrics will be held June 7 and 8, 1935, at the Waldorf Astoria Hotel, New York City

The program has been announced as follows

Friday, June 7, Panel Discussions.

- 9 30 A.M.—'Indications for Surgery in Pyuria,' Chairman Dr Hugh Cabot
Rochester, Minn.
- 11 00 A.M.—'Prevention of Colds in Children,' Chairman, Dr Lee Wallace Dean, St
Louis, Mo.
- 2 00 P.M.—Round Table Discussions.

Subject	Leader
'Adolescence'	Dr Borden S. Vedder
'Bacillary Dysentery '	Dr Wilburt C. Davison
'Blood '	Dr Thomas B Cooley
'Chronic Lung Conditions	Dr Isaac A. Abt
'Diabetes'	Dr Henry B. Geyelin
'Eczema'	Dr Lewis Webb Hill
'Encephalitis '	Dr Josephino B. Neal
'Heart '	Dr Hugh McCulloch
'Newborn '	Dr Arthur H. Parmelee
'Osteomyelitis '	Dr Arthur Krida
'Pollomyelitis	Dr John A. Toomey
'Prematurity '	Dr Julius Heas
'Tuberculosis	Dr Chester A. Stewart
'Whooping Cough '	Dr William H. Park
'Recent Advances in Nutrition '	Dr H. C. Sherman

8 00 P.M.—Joint meeting of state chairmen and the committees on child health relations, school health and school health education, and hospitals and dispensaries.

Fellows are invited but are not permitted to join in the discussion except through state chairmen

Saturday June 8

9 30 A.M.—General Meeting

President's address

Report of the executive board

Report of secretary treasurer

Report of regional committees

Report of special committees.

(Reports will be presented in mimeograph form to the membership)

Panel Discussions

2 30 P.M.—'Pituitary Glands, Chairman Dr R. G. Hoskins Boston Mass.

4 00 P.M.—'Nutrition,' Chairman, Prof. E. V. McCollum, Baltimore Md.

There will be approximately twenty five commercial and five scientific exhibits. These will be in the registration room and the Jade Room through which one must pass to go to the meeting hall.

An announcement concerning railroad rates will be made later

All members should make reservations for hotel accommodations. Special registration cards will be given all members. Regardless if they stay at the hotel prior to the convention or immediately following the meeting, the same special schedule of rates will apply.

Dr. Harry C. Berger, Kansas City, Mo., has accepted the state chairmanship for Missouri.

Dr. Sterling H. Ashmun, Dayton, Ohio, has been appointed state chairman for Ohio.

News and Notes

Members of the American Committee for the International Pediatric Congress to be held in Rome, Italy, in 1936, are as follows:

American Pediatric Society: Dr. Henry F. Helmholtz, Dr. Clifford G. Grulec, and Dr. L. Emmett Holt, Jr., secretary of the American committee.

American Academy of Pediatrics: Dr. C. Anderson Aldrich, Dr. L. R. DeBuys, and Dr. Clifford G. Grulec.

Section on Pediatrics of the American Medical Association: Dr. Fred W. Schlutz, Dr. Alexis F. Hartmann, and Dr. Frank C. Neff.

Those who have been chosen so far by the committee to appear at the Congress are: Dr. James L. Gamble, "Relator" on the subject, "Mineral and Water Metabolism in Childhood and Its Relation to the Problem of Artificial Feeding"; Dr. Chester Stewart, "Relator" on the subject, "The Problem of Childhood Tuberculosis"; and Dr. Bronson Crothers, "Correlator" on the subject, "Neuro-psychiatric Diseases in Pediatrics From the Clinical and Social Point of View."

The Society for Pediatric Research will meet on Tuesday, May 7, 1935, at the Chilfente-Haddon Hall in Atlantic City. There will be a morning and afternoon program. Dr. A. A. Weech of New York is secretary of the Society.

The American Pediatric Society will hold its annual meeting at the Wade Park Manor in Cleveland, Ohio, on May 2, 3, and 4, 1935. Dr. Hugh McCulloch, of St. Louis, is secretary of the Society.

The Section on Pediatrics of the American Medical Association will meet in Atlantic City at the time of the general meeting, June 12, 13, and 14, 1935. This meeting will be a joint one with the Canadian Medical Association, and it is expected that the meeting of the scientific assembly will be a most unusual one.

The South Carolina Pediatric Society held its annual meeting at the Jefferson Hotel, Columbia, S. C., on Monday, February 11, 1935. Dr. E. C. Mitchell, of Memphis, Tenn., was a guest of the Society and conducted a round table discussion on the subject, "Tonsils." A motion was carried that the attitude of the Society on this question should be made public in the lay press of the state and also to the state medical association. Approximately 87 per cent of the pediatricians of South Carolina were present, as well as many otolaryngologists.

Dr William Weston, Jr, of Columbia, was elected president Dr Thomas Dotterer of Columbia vice-president, and Dr Leland Saltera, of Florence was re-elected secretary treasurer

A recent meeting of the Texas Conference on Child Health and Protection was held with Dr E. G. Schwarz, of Fort Worth, as chairman of the medical section. He was assisted by Dr T. J. McElhenny, Austin, Dr L. O. Godley Fort Worth, Dr Mary Harper San Antonio Dr Howard Granberry Austin, Dr M. S. Wheeler Austin Dr Edythe P. Hershey Dallas, and Dr C. D. Beece of the State Health Department. The meeting was well attended and the program well received by the lay workers present

May Day Child Health Day has become an established institution throughout the United States. It was inaugurated in 1924 by the American Child Health Association for the purpose of calling the attention of parents, communities, and the public in general, to the need for measures to protect the health of children.

In 1928 the United States Congress passed a joint resolution designating May 1 as Child Health Day and authorizing the president to issue a proclamation requesting national observance of the day.

In 1929 the Conference of State and Provincial Health Authorities of North America appointed a May Day Committee, which in 1932 took over from the American Child Health Association with the continuing assistance of that organization, the responsibility for the annual observance of Child Health Day. In the states the work is under the direction of state departments of health.

The May Day Child Health Day project for 1935 is diphtheria immunization. It was chosen because there has been but little reduction since 1930 in the number of deaths from diphtheria throughout the country.

Immune now—stamp out diphtheria is the slogan.

The measures proposed are

To immunize all children between the ages of six months and six years.

To make early immunization a routine practice by physicians in the future.

The goal of the work is *no deaths from diphtheria*.

In order to obtain the cooperation of physicians, it was suggested to each state health officer that he send a communication to each physician in his state urging

That he remind his patients who have children under school age of the need for immunization

That he ask his patients to bring their children to be immunized

That in the future he make it a routine of his practice to immunize during the first year of life all babies under his care.

Many state health officers have responded enthusiastically to this suggestion. The majority of pediatricians do immunize early as a matter of routine. It is desired that physicians in general practice do likewise. Plans for this should be worked out by local medical societies in conjunction with the departments of health. Members of the American Academy of Pediatrics have been asked to assist.

This project will tend to place the responsibility for diphtheria immunization on the physicians, where it rightly belongs. Each member of the American Academy of Pediatrics should be counsellor and guide in this work in his own community.

The following men have been certified by the American Board of Pediatrics since the last report

Louis H. Barenberg New York N. Y.

Stanley Brady New York, N. Y.

F. H. Clark Jamestown N. Y.

Harry O Davidson, Detroit, Mich.
 Clair L Douglas, Detroit, Mich.
 Ethel Collins Dunham, New Haven, Conn
 William Littell Funkhouser, Atlanta, Ga.
 Linton Gerdina, Athens, Ga.
 Jesse Robert Gerstley, Chicago, Ill
 Murray Burnes Gordon, Brooklyn, N Y
 Benjamin Hoyer, Cincinnati, Ohio
 W Lloyd Kemp, Detroit, Mich
 George Clifford King, Fall River, Mass
 James Hall Mason Knox, Jr, Baltimore, Md
 A Max Kohn, Detroit, Mich.
 John Allison Nunn, San Antonio, Texas
 Harry D Pasachoff, New York, N Y
 Donald Wallace Porter, New Haven, Conn
 L J Schermerhorn, Grand Rapids, Mich
 Philip H Sylvester, Boston, Mass

Correspondence

London, W 1, February 16, 1935

Comment was made last May on the subject of malnutrition and physical unfitness in children in relation to the economic difficulties existing in certain sections of the population in England at the present time. In this connexion the recently published annual report of Sir George Newman, Chief Medical Officer to the Board of Education, is of interest. During the year covered by the report, 3,000,000 school children passed under medical review, and 2,000,000 re-inspections were carried out. Three hundred and sixteen local educational authorities submitted figures, from which the mass return of 1933 was compiled, and it shows that the condition of school children throughout England and Wales during this period demonstrated no deterioration when compared with the two preceding years. Sir George Newman therefore concludes that, in spite of distressing economic and social difficulties, the general health and nutrition of school children has on the whole been well maintained.

It should be mentioned in this connexion that two committees set up to investigate and report upon the question of diets adequate for the maintenance of good health recently issued their reports, which gave rise to some controversy. The one committee appointed by the Ministry of Health regarded as adequate a dietary containing rather less first class protein and somewhat lower in total caloric value than that recommended by a similar committee appointed by the British Medical Association. Both committees numbered among their members persons of unquestionable authority on the subject under investigation. As might be expected, political capital was made of the fact that the scale was lower in the report issued by the committee of the Ministry. However, it was obvious to a critical scientific observer that the differences between the two reports were more apparent than real, and the wise course was adopted of arranging a meeting between representatives of both committees. As a result a statement was issued making clear the reason for the differences which existed, and thus showing cause for dispute. One of the points of difference was in regard to the question of increased amounts of milk for children, advocated by the British Medical Association committee, and at the present moment it has been conceded that any school teacher can authorise the provision of free

milk to be given at school to a child considered to be under nourished, pending the next school medical inspection, when the medical officer in charge will review the case.

As is probably well known, a further effort is being made by the osteopaths to obtain official registration and state recognition in this country. The bill aimed at effecting this has just passed its second reading in the House of Lords. The Lord Chief Justice, in the course of the debate said that as a mere lawyer he was staggered by the bill which among other things, would allow an osteopath to sign a death certificate. Lord Moynihan and Lord Dawson (President of the Royal College of Physicians) both opposed the bill, pointing out from a professional point of view the monstrosities of the measure and the adverse influence it would have on the interests of the laity themselves. The medical profession generally is entirely opposed to the registration of osteopaths, who appear by the terms of the bill to be trying to create a method of carrying out medical practice in its fullest sense without having conformed with the minimum requirements of the General Medical Council. After once obtaining a legal medical qualification in the usual manner a practitioner is allowed to practise in this country any method he may choose, but any attempt to obtain full recognition to practise without ordinary preliminary and clinical training appears to be a back-door method of entering upon medical practice, and a dangerous one.

The Goulstonian Lectures, three in number, are to be given this year in March, before the Royal College of Physicians, by a paediatrician, Dr Alan Moncrieff his subject being "Respiratory Failure, Including the So-called Asphyxia Neonatorum".

During this winter the meetings of the Children's Section of the Royal Society of Medicine, under the presidency of Dr R. Jewsbury, have maintained their past standard of clinical interest and one new feature has been the devoting of one meeting to the re-showing of cases previously demonstrated and discussed.

The British Paediatric Association is meeting this year on the third and fourth of May, at Newcastle County Down, in Northern Ireland. Dr Hugh Thursfield is this year's President, and Dr A. G. Maitland Jones is now the Secretary. This will be the first meeting of the Association to have taken place in Ireland.

K. TALLERMAN

Erratum

On page 40 of the article, 'Hemorrhage and Subsequent Calcification of the Suprarenal,' by Charles E. Snelling M.B., and I. H. Erb, M.B., the third sentence in the fifth paragraph of the summary should read, 'In the *sight* with calcification there was definite evidence of previous hemorrhage into the gland

Comments

THE truth of the frequently repeated statement that the high maternal mortality rate of the United States when compared with the rate for foreign countries was due in a large part to differences in recording deaths, and hence was not real, has been rudely shattered by a recent study of the Children's Bureau*. In continuing a study of the Third White House Conference, a sample group of 1,073 deaths occurring in 1927 and certified by attending physicians as puerperal were selected and the pertinent information from 477 of these sent to the vital statistics division of twenty four foreign countries, with the request that they be classified in accordance with their rules and regulations for classifying deaths. No information as to how they had been classified in the United States reports was given. Replies were received from sixteen countries. The rate for the United States was then checked according to the way the deaths in the United States would have been recorded in each country. In this way a definite basis of comparison between the United States and foreign countries was established.

The rate for the United States remains at the top of the list, 64.7 per 10,000 live births. Scotland has practically the same rate, 64.3. Norway has the lowest rate, 24.5. Next lowest comes Italy, Sweden, and France with 26.4, 27.8, and 28.7, respectively. The rate for England and Wales is 41.1 and for Canada, 55.5. It is thus quite obvious that differences in method of assignment are insufficient to explain the high maternal mortality rate in the United States. Differences in live births as well as differences due to incompleteness of birth registration are negligible factors in the maternal mortality rate. The problem returns to one of medical care and oversight or, in brief, better obstetrics.

AS A rule it is not the policy of the Journal to publish long papers such as the study of fat metabolism which appears in this issue. The Editorial Board felt that this particular study by Dr. Holt and his associates was so thorough and of such fundamental importance that it ranks as one of the best contributions that has appeared from an American pediatric clinic. Arrangements were therefore made to increase the size of this number of the Journal so that the usual variety and scope of contributions should not be curtailed because of the length of this particular paper.

THE American Child Health Association is sponsoring diphtheria immunization for its 1935 May Day project. Its plans are formulated along the line of urging parents to take their preschool children to a physician for immunization. Members of the Academy are requested to help in working out the local state and community programs.

*Comparability of Maternal Mortality Rates in the United States and Certain Foreign Countries. Elizabeth C. Tandy, D.Sc. Bureau Publication No. 229. Children's Bureau, Dept. Labor, Washington, D.C. 1935.

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Original Communications

FACTORS INFLUENCING THE EFFECTIVENESS OF PLACENTAL EXTRACT IN THE PREVENTION AND MODIFICATION OF MEASLES

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AND HARRIET COADY
BOSTON MASS

INTRODUCTION

A REVIEW of the recorded observations regarding placental transmission of immune bodies from mother to offspring, and the demonstrable presence of various antibodies in the umbilical cord blood of infants¹ led to the concept that protein extracts of the placenta might be prepared which would be capable of increasing the protective reaction of infants and children to certain disease processes. Early in our studies it was found that such extracts could be prepared and that by qualitative tests they contained substances, presumably antibodies which would neutralize diphtheria toxin, blanch scarlet fever rashes, neutralize poliomyelitis virus, and prevent measles in exposed, susceptible patients.²

It is the purpose of the present communication to report the progress which has been made in further investigation of these extracts, particularly as regards the factors influencing the practical application of the material on a larger scale to the prevention and modification of measles.

The value of convalescent measles serum or pooled adult immune serum in the prevention and modification of measles has been amply demonstrated. The clinical application of these substances has been hampered by the lack of an adequate supply of convalescent serum and by a marked variation in potency, particularly of adult immune serum. Despite occasional failures, convalescent serum and adult immune

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This study was supported in part by a grant from the Commonwealth Fund of New York.

serum have been extensively used for the control of the disease in ill or debilitated children, especially in institutions. Placental extract held the promise of solving the problem of the supply of the immune substance. Whether the extract could be standardized to give uniformly predictable results has been a major object of investigation.

The presence of several factors which influence the effectiveness of a serum in the control of measles complicates the problem of standardization. It has been thought that (1) potency and (2) dosage of serum in terms of nitrogen concentration of the active fraction in relation to (3) the time of injection were the important items, whether one was dealing with convalescent serum, adult blood, or a preparation like placental extract. However, (4) age and size of the patient and (5) degree of exposure are probably factors, although it is difficult to establish quantitatively their importance. If the potency of the preparation could be standardized, dosage could be adjusted for age and size so that the time of injection of extract would become the factor determining the effectiveness of treatment.

Placental extract has been found in previous studies to be comparable to fresh convalescent serum in that a potent extract given to a nonimmune person in adequate dosage within four days after exposure resulted usually in protection, whereas extract given in the same dosage later in the period of incubation resulted in modification of the disease.³

In the attempt to secure uniformly potent extracts, the effect of a variation in antibody content of individual placentas has been overcome by pooling placentas in large lots. The effectiveness of the crude unfiltered globulin extracts had been found to be surprisingly uniform. Crude preparations had been used in 118 susceptible patients exposed to measles without any failures to secure prevention or modification of the disease. However, the crude preparations could not be passed through a Berkefeld filter and, despite repeated tests for sterility, were not deemed to be entirely safe. Consequently an effort was made to determine the fractions of extract which would pass the filter and still be effective against measles.

NOTES ON METHOD OF PREPARATION OF PROTEIN FRACTIONS

Normal appearing placentas from nonsyphilitic and nontoxic mothers were collected in lots containing from eight to fifty placentas. The umbilical cords were tied to prevent loss of the fetal blood contained in the organs. In earlier preparations the placentas were cut into small pieces with an amputation knife, in later studies the organs were ground very fine in a food chopper. Extraction was carried out with 4 per cent salt solution, in the earlier work 2 per cent had been used. Hypertonic saline was used in order to minimize hemolysis, which occurs rapidly in umbilical cord blood and in the placental extract prepared in isotonic salt solution. About 300 cc of the salt solution was added for each placenta. The material was stirred mechanically for half an hour, and at the end of this time the tissue

débris was removed by filtration through cheesecloth after which the blood cells were removed by centrifugation. Extraction of each lot was repeated once or twice so that the total amount of saline used was from 750 to 1,000 c.c. per placenta.

Such extracts contained fetal blood, some maternal blood and a quantity of placental tissue protein. Because of the association of immune bodies with the globulins of the blood serum of lower animals and presumably of humans, a concentrate of the active material and the removal of inert or noxious matter was sought by separation of the globulin fractions through precipitation with ammonium sulphate. Tests for toxicity and sex hormones indicated that the globulins contained a negligible amount of the hormones and that they were nontoxic for animals even if injected in large doses. Also, by animal tests and clinical trial the antibodies sought were found to be present in the globulin fractions.

Separation of the globulin fractions was carried out by the addition of a saturated solution of ammonium sulphate in such amount as to bring the concentration of the salt up to 50 per cent saturation. The precipitate which formed was collected on filter paper. The filtrates were discarded. The precipitate was dried between folded filter papers and was then redissolved in salt solution. Reprecipitation served to eliminate in large measure hemoglobin carried down with the globulins.

The final precipitate was placed in cellophane tubes, dialyzed against running water for twenty four to thirty six hours, and then against isotonic saline until sulphate-free. The dialyzed extract was adjusted to pH 6.8 (blue green to brom thymol blue). The extracts were somewhat cloudy or muddy appearing suspensions from which a precipitate settled out; this was sometimes centrifuged off and tested separately, designated fraction 'FP'. Part of the activity against measles was lost in this sediment. The supernatant was put through a Berkefeld V candle after the addition of 15,000 morpholine. Filtration was very difficult, with a further considerable loss on the candles of the material effective against measles.

The fraction obtained by precipitation with one-half saturated ammonium sulphate and containing practically all of the globulins and little albumin has been designated fraction 'T'.

Subsequently the globulins were separated into two fractions. To prepare the first, or euglobulin fraction, sufficient of the saturated solution of ammonium sulphate was added to the placental extract to bring the final concentration up to 28 per cent saturation. The precipitate formed was collected on filter paper. To the filtrate obtained there was added saturated ammonium sulphate solution to bring the concentration of ammonium sulphate up to 50 per cent saturation. The precipitate obtained by the addition of ammonium sulphate solution to make 28 per cent saturation was very small in amount and difficult to remove from suspension by filtration. Part of this precipitate was insoluble in salt solution. The soluble portion, representing largely euglobulin, was designated fraction 'U'.

The precipitate obtained with ammonium sulphate between 28 per cent saturation and 50 per cent saturation was quite large in amount and tended to settle out of suspension in a few hours. This precipitate was readily collected on filter paper and appeared to be soluble in physiologic solution of sodium chloride or in Ringer's solution. It was largely pseudoglobulin and was designated fraction 'M'.

A clear solution which filtered very rapidly could be prepared by removing a water-insoluble fraction at about pH 5.5. This was done by diluting the above final product to eight times its volume with distilled water and adjusting the pH with weak HCl. The isoelectric precipitate so obtained was redissolved and reprecipitated at least once to make the separation more accurate. The filtrates were reprecipitated with ammonium sulphate at one-half saturation, and the precipitate again dialyzed as before. Activity in the prevention of measles was impaired by removal of the isoelectric precipitate.

The isoelectric precipitate removed before separation of the other globulins was designated fraction "P" The 0 to 50 per cent ammonium sulphate precipitate with isoelectric precipitate P removed was designated fraction "S," and that from 28 to 50 per cent precipitation designated fraction "R"

If the original saline extract diluted with sufficient water to lower the salt concentration to 1 per cent was acidified with HCl to pH 5, a heavy flocculent material formed which settled out readily on standing This fraction was designated "TG", it was a tissue protein, obtainable only in minute amounts from the blood serum. It was soluble in hypertonic saline and in weak alkalis.

In summary the various fractions investigated, all presumably globulins, have been two ammonium sulphate precipitates, corresponding roughly to pseudoglobulin (fraction R), and euglobulin (fraction U), an isoelectric precipitate (fraction P), and a fraction insoluble in acidified normal salt solution but soluble in hypertonic saline and in alkaline solutions, fraction TG Various combinations of these fractions have also been prepared

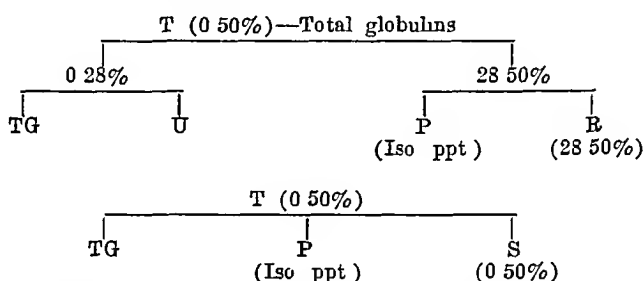


Fig 1—Derivation of the various globulin fractions investigated for antibody content. The percentages refer to concentrations of saturated ammonium sulphate used as the precipitating agent.

In Fig 1 is shown diagrammatically the derivation of the various fractions

For further clarity the designations employed for the fractions and the combinations are given in Table I

TABLE I
PLACENTAL GLOBULINS

<i>Total globulin</i>	
T	= ppt in 0.50% $(\text{NH}_4)_2\text{SO}_4$
<i>Euglobulins</i>	
TG	= ppt in acidified 1% NaCl—derived largely from tissue
P	= ppt in acidified 0.1015% NaCl—partly from serum and partly from tissue
U	= ppt. in 0.28% $(\text{NH}_4)_2\text{SO}_4$
<i>Pseudoglobulins</i>	
M	= ppt in 28.50% $(\text{NH}_4)_2\text{SO}_4$
R	= M with P removed
S	= T with P and TG removed

It is to be emphasized that not all the fractions have been obtained in pure form a differential precipitation is inadequate for complete separation because the demarcation between the types is not a sharp line, but is rather a zone. Thus in the preparation of any fraction some overlapping of the protein above and below is likely to occur. In the search for the substance active against measles efforts were made to determine any association of the various immune bodies with distinct fractions.

DISTRIBUTION OF ANTIBODIES IN VARIOUS FRACTIONS

Although complete separation of the fractions has not been possible the investigation of the association of antibodies with the individual fractions has yielded interesting results. Tests for the diphtheria toxin neutralizing capacity could be made readily on animals, and it was hoped that the diphtheria antitoxin content would parallel other antibodies and that the determination of this substance in various lots of extract might give evidence as to the degree of concentration obtained in the process of preparation, as well as of the potency of other antibodies, notably those like measles which could not be tested for in the experimental animal. The substance neutralizing diphtheria toxin was found to be largely in the pseudoglobulin fractions with small amounts only in the euglobulins. In an especially purified euglobulin made by repeated precipitations of a water insoluble fraction derived from a 28 per cent ammonium sulphate precipitate, no diphtheria antitoxin could be demonstrated. Similar results were observed in the search for the substance active in blanching scarlet fever rashes. Mild local reactions to the intracutaneous injections of the extract interfered considerably with this test. However in cases in which local reactions to the intradermal injection of placental extract did not occur the blanching substance was found to be present almost exclusively in the pseudoglobulin fractions. Placental extract did not produce blanching of simple erythemas, heat rashes or drug rashes. Attempts were made to titrate the neutralizing effect of the extract on Dick toxin by injecting intradermally dilutions of the fraction under investigation mixed with standardized doses of commercial Dick toxin. These tests were also clouded somewhat by the tendency of the injection of the extract alone to cause local redness. More striking results have been obtained in attempts to reverse the Dick reaction of patients. Injections of 5 to 10 c.c. of placental extract subcutaneously or intramuscularly into patients with positive Dick tests were found to be followed by a period of several days during which repeated Dick tests were negative. This observation has been made independently by Ross.⁴

In addition to the substance producing blanching of scarlet fever rashes and reversing the Dick reaction, the crude extract was found

to contain an active antistreptolysin. The investigation of the location of this antibody has not been pursued.

From the above observations it became evident that diphtheria antitoxin and scarlet fever antitoxin were to be found almost exclusively in the pseudoglobulin fractions. However, the anticipated parallelism between these antibodies and those to the virus diseases, poliomyelitis and measles, was not observed. On the contrary the virus antibodies, as exemplified by antimeasles activity, were present in roughly comparable amounts in each of three fractions, the euglobulin, the pseudoglobulin, and the isoelectric precipitates. That part of the tissue protein which was insoluble in physiologic salt solution has not been tested in the prophylaxis of measles because of its lack of solubility and the accompanying difficulty of rendering this fraction sterile.

The distribution of antibodies against poliomyelitis was similar to the distribution of the antibodies against measles. As a result of fourteen neutralization tests, it may be stated definitely that in routine lots both the euglobulin and pseudoglobulin fractions may be expected to contain the poliomyelitis virus neutralizing substance. The tissue protein fraction which is insoluble in 1 per cent saline is also able to effect neutralization. Preserved lots of the various fractions were used in the later neutralization tests after it had been observed that merthiolate 1:5,000 in normal horse serum failed to neutralize the poliomyelitis virus. This finding, together with the fact that one of the fractions even in the presence of the preservative failed to neutralize the virus, indicated that any effect of the preservative on the virus with resultant neutralization falsely attributed to the serum, might be disregarded.

In the present communication only the data regarding the effectiveness of the various fractions in the prevention and modification of measles will be given in any detail.

EFFECTIVENESS OF THE VARIOUS FRACTIONS IN THE PREVENTION AND MODIFICATION OF MEASLES

In the period extending from the time of the inception of the study until Dec 5, 1934, 1,258 nonimmune children exposed to measles have been given various fractions of placental extract in an effort to prevent or modify the disease. One thousand and eleven of these patients received extracts made in this laboratory, while 247 received an extract prepared commercially. The results of this study are shown in Table II.

It is to be noted in the figures representing the total number of patients treated that the percentage in which protection and modification were obtained was much the same with the commercial preparation as

with our own material. This is of particular interest because the commercial product represented a single type of preparation similar to our S fraction.

TABLE II
PLACENTAL EXTRACT FOR PREVENTION OR MODIFICATION OF MEASLES
TOTAL CASES TO DEC 5 1934

SOLUTION (OR FRACTION)	CASES	PROTECTION		MODIFICATION		FAILURE	
		NO.	%	NO.	%	NO.	%
T (0-50)	182	159	87.4	10	10.4	4	2.20
M (28-50)	413	294	71.2	93	22.6	25	6.00
R (28-50)S	09	82	82.8	12	12.2	5	5.00
S (0-50)	181	125	69.2	51	28.0	5	2.76
P Iso. ppt.	100	59	50.0	31	31.0	10	10.00
FP Iso ppt. removed at end	37	22	59.3	14	38.0	1	2.70
Total	1011	741	73.2	220	21.8	50	5.00
Commercial extract	247	181	73.3	58	23.4	8	3.20
Total cases	1258						

As noted above the crude unfiltered preparation containing all the globulins (fraction T not filtered) had shown no failures in over one hundred cases. Passage of this material through a Berkefeld filter resulted in a considerable loss of the activity. It is to be noted further that no fraction was obtained which equalled the effectiveness of the crude material or the filtered T preparation although it would appear that the R fraction (pseudoglobulin) was most nearly comparable in activity and that the P fraction (isoelectric precipitate) was the weakest. However the differences in the activity of the proteins are more apparent than real because in this table variation in dosage on the basis of total nitrogen content is not considered nor are the degree of exposure and time of injection given weight.

In order to clarify the factor of degree of exposure and to eliminate the possible inclusion in the total figures of children only questionably exposed to the disease the total number of cases was subdivided into three groups:

1 Intimate exposure—children exposed at home to a brother or sister or to a roommate in a boarding school—all types of exposure in which upward of 90 per cent of nonimmune children could be expected to acquire the disease.

2 Institutional exposure—such as in the hospital where only about one-third of the nonimmune contacts would acquire the disease on exposure to a single case.

3 School exposure—in which contact is casual and infection can not be presumed to have occurred.

All cases of modified measles and all complete failures of protection in Group 3 were transferred to Group 1, inasmuch as this development demonstrated that such patients had actually been infected with the disease. This procedure obviously swelled the number of failures

and modifications in Group 1 in proportion to the number of complete protections. However, the procedure served to make the test of the extract more stringent. Group 1 represents then the most severe test of the extract. In Table III are shown the results in Group I (intimate exposures) of the use of various fractions of placental extract in the prevention and modification of measles. The cases in this group are also subdivided on the basis of time of administration of extract, so far as the duration of exposure was accurately known. "Given to protect" meant given within four days after onset of exposure. "Given to modify" meant that extract was given from five to nine days after exposure with the intent not of securing protection but of modifying the course of the disease.

TABLE III
INTIMATE EXPOSURE

SOLUTION (OR FRACTION)	CASES	GIVEN TO PROTECT			GIVEN TO MODIFY		
		P	M	F	P	M	F
T (0.50)	26 25	21	5	0	13	9	3
M (28.50)	47 149	26	14	7	67	67	15
R (28.50)S	16 19	13	3	0	12	5	2
S (0.50)	29 49	22	6	1	12	35	2
P Iso ppt.	16 36	5	9	2	9	21	6
FP	9 13	2	6	1	5	8	0
Commercial preparation	24 102	12	11	1	68	30	4
Total	560	101	54	12	186	175	32
Percentage -----		60.5	32.3	7.2	47.3	45.5	7.2
Percentage -----		92.8			92.8		

Here again fractions T and R appear somewhat more satisfactory than other portions. It is obvious that the active principle is present in all fractions tested and that each attempt at refinement has resulted in a weakened product. However, these various fractions differed considerably in milligrams of nitrogen per cubic centimeter. The P fraction was particularly low in nitrogen, not because the isoelectric precipitate itself was small in amount, but because the precipitate was so insoluble and difficult to filter. In preparing P fractions for clinical trial, most of the protein was left on the filter candles. The marked variation in nitrogen content of the filtered extracts necessitated a review of the data and a reappraisal of the effectiveness of the various fractions in terms of protein administered in a single dose as measured by milligrams of total nitrogen. The results of this appraisal are shown in Table IV.

The effectiveness of the fractions is considered in relation to dosage of material in terms of nitrogen and with variations in size and age of the patients. It is to be noted that, since the activity of the fractions in terms of nitrogen content was roughly equal, it would appear that the activity as regards measles is distributed throughout the frac

tions Furthermore it is to be noted that for children under two a dosage of 20 to 30 mg of nitrogen was adequate, but for older children this amount of material was insufficient

TABLE IV
NITROGEN DOSAGE AND EFFECTIVENESS

	FRACTION	MG N 5-20			MG N 21-30			MG N 31--		
		P	M	F	P	M	F	P	M	F
Patients 6 mo. to 2 yr	T	4		1	4			20	2	
	M	20	5	2	43	7		13		1
	R	3	1	2	2	2		6		
	S	8	31		9	1		3	3	
	P	8	6	3	10	1		8		
	FP	1			2			1	1	
Total		44	43	8	60	11	0	51	6	1
Percentage		46.5	45.3	3.5	69	11	0	88+	10.3	1.7
Patients over 2 yr of age	T	13	5	2	32	6	2	78	5	0
	M	38	10	9	117	44	8	63	19	4
	R	2	1		5	3	1	22	8	2
	S	17	8		34	10		34	18	2
	P	32	17	7		7		1		
	FP	1			4	1		13	12	1
Total		105	41	18	192	71	11	211	57	9
Percentage		64	25	11	70	26	4	76.1	20.7	3.2

REACTIONS

The incidence of reactions of both mild and severe type which followed the injections of the various protein fractions is shown in Table V. It will be seen that 23 per cent of the patients had mild local

TABLE V
REACTIONS

FRACTION	TOTAL NO. PATIENTS	NO REACTION		LOCAL		FEBRILE		LOCAL++		FEBRILE (TEMP 101 + F)	
		NO	%	NO	%	NO	%	NO	%	NO	%
T	207	142	70.0	36	18.0	40	20.0	5	2.4	9	4.4
M	433	314	72.0	99	23.0	35	8.0	8	1.8	4	0.9
R	144	112	78.0	21	14.0	14	10.0	1	0.7	2	1.4
S	228	164	72.0	60	26.0	19	8.0	8	3.5	2	0.9
P	137	71	51.7	56	41.0	82	23.0	10	7.8	5	3.6
	1,149	803	70.0	272	23.7	140	12.4	32	2.8	22	1.9

reactions and that 12 per cent had slight general reactions as indicated by fever. The incidence of severe local reactions was 2.8 per cent and of more severe febrile reactions (indicated by an elevation of temperature over 101 F), 1.9 per cent. In no instance did a local reaction persist longer than four days, and in no instance did suppuration occur.

The percentage of reactions was approximately the same for both boys and girls. Age seemed to affect the incidence of reactions in

that reactions were more frequently encountered among older children and adults than among infants and younger children. It is noteworthy that the P fraction, with about half the protein concentration of the other fractions, gave the highest incidence of reactions. This has been attributed to the larger amount of tissue protein in the P fraction. Such an assumption is borne out by the observations from later studies in which methods of extraction were used which resulted in an increase of the tissue protein in the material. The lots from which this tissue protein was not removed caused more reactions than did the lots in which the proteins injected resembled more nearly the blood proteins.

In pursuing this subject the studies of Wooldridge⁵ and Mills⁶ regarding the coagulative action on the blood of tissue proteins were reviewed. The protein derived from lung tissue and designated by Mills as "tissue fibrinogen" is chemically and physically very similar to our 1 per cent acidified saline precipitate, so-called fraction TG.

Sakurai⁷ in 1929 prepared extracts from the human placenta and found that they had the same powerful coagulative action on blood as did animal tissue extracts. Not only would inclusion of certain of the tissue proteins probably be responsible for part of the reaction to the material, but their presence would obviously render the material unsafe for intravenous administration. Filtration seems to remove the bulk of the substance which acts as a coagulant. However, placental extract has not been used intravenously in humans because of this potential danger, although it has been given to rabbits and monkeys in large doses without serious effects. The influence of placental tissue extract on blood clotting will be reported in a subsequent paper.

Immediate and late allergic serum reactions presumably should not occur with a protein of human origin. Nevertheless, three cases of accelerated serum disease occurred among the total number of patients receiving placental extract. Two of these reactions occurred in children known to be allergic, the third child had no previous allergic history.

Injections of placental extract have been found not to sensitize to subsequent injections of the material. A number of patients have received two or more injections at intervals varying from a few weeks to several months. In no instance were the second or subsequent injections followed by local reactions of more severity than were observed after the first injection, and in no instance were there any manifestations of specific sensitization. These findings are in accord with the observations of Nattan-Larrier and Grimard-Richard that fetal serum has no sensitizing action on adults of the same species.⁸

DURATION OF IMMUNITY

Immunity following the injection of placental extract is passive in type and is of short duration. In Table VI are shown results of reexposure of eighteen children within a few weeks after receiving placental extract.

TABLE VI

DURATION OF IMMUNITY
PERIOD BETWEEN INJECTIONS OF EXTRACT AND SUBSEQUENT EXPOSURE

	2 WK.	3 WK.	4 WK.	5 WK.	6 WK.	7 WK.
Number of patients	1	6	6	2	2	1
	Disease modified		Disease not modified			

Eighteen patients were exposed, received extract, and were reexposed.

The time in weeks indicates the period between injection and subsequent exposure.

In view of the short duration of immunity it is doubtful if injection of the material to protect a patient is justifiable outside of institutions except in the case of debilitated tuberculous, or other acutely or chronically ill children. Rather, the extract should be used to modify the disease and presumably thereby to render the patient permanently immune. That permanent immunity follows modified measles is generally believed, but the number of patients which have been followed is small, so that among the problems that must be solved is the one of how much modification or how little modification of measles will still permit the development of permanent immunity. It is known that, if no measles develop after the administration of serum, the patient again becomes susceptible within a period of a few weeks whereas, if the typical disease develops, the patient is usually rendered permanently immune. Somewhere between the state of no symptoms and the typical disease lies a stage of enough illness not to endanger the life of the patient, yet to render the child permanently immune. With large-scale studies of measles modification the answer to this question should be found. Modified measles is not known to be followed by complications which render the unameliorated disease a menace. However, here again adequate data on which to base a positive statement are not available.

SUMMARY

Placental extract can be prepared in large amounts and can be made available for the large scale prevention or modification of measles. Attempts to refine and concentrate the measles antibody have resulted in preparations of less potency than the extracts containing all of the globulins. However, the refined preparations can be passed through Berkefeld filters and may therefore be deemed safer to use.

The results in a series of 1258 cases demonstrate that the refined extracts although less active than the crude preparations, are still effective.

tive in the prevention or modification of measles. However, this number of tests is inadequate to permit the determination of the best fraction of the extract to use and the dosage required in children of various ages and at various stages of the incubation period of the disease.

The scarlet fever and diphtheria antibodies in placental extract appear to be almost entirely in the pseudoglobulin fraction, whereas the measles and poliomyelitis antibodies appear to be distributed throughout several protein fractions. The tissue protein insoluble in acidified salt solution contains no diphtheria antitoxin but does contain the antibody neutralizing poliomyelitis virus. It has not been tested for activity against measles.

Reactions following the injection of placental extract, although infrequent, appear to be due in some measure to the inclusion in the finished extract of variable amounts of a specific tissue protein. A method of preparation and administration of extract to eliminate reactions is at present under investigation.

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OBSERVATIONS ON THE THERAPEUTIC VALUE OF SPECIFIC IMMUNE SERUM IN EXPERIMENTAL POLIOMYELITIS

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IT IS well established that the serum from monkeys having recovered from poliomyelitis is capable of neutralizing the virus in vitro (Levaditi and Landsteiner,¹ Leiner and von Weisner,² Römer and Joseph,³ Flexner and Lewis,⁴ and others) This property is also exhibited by the serum of human beings following recovery from acute poliomyelitis (Netter and Levaditi,⁵ Flexner and Lewis,⁴ and others) Not only human poliomyelitis convalescent serum but also the serum of a considerable percentage (about 75 per cent) of the adult population who have to their knowledge not had poliomyelitis may exhibit this property (Aycock and Kramer,⁶ Shaugbnessy Harmon, and Gordan,⁷ Schultz and Gebhardt,⁸ and others) Besides man and monkeys, individual animals in the poliomyelitis refractory group (e.g. sheep, goats, and horses) may respond to repeated injections of poliomyelitis virus with the production of a virucidal serum of more or less high antibody content (Neustaedter and Banzhaf,⁹ Pettit,¹⁰ Weyer, Park and Banzhaf,¹¹ Fairbrother,¹² Fairbrother and Morgan,¹³ Howitt,¹⁴ and Schultz and Gebhardt¹⁵)

This paper deals with the therapeutic value of poliomyelitis immune serum in the *experimental disease*

REVIEW OF THE LITERATURE

Comparatively little work on the therapeutic* value of immune serum in experimental poliomyelitis has thus far been reported Levaditi and Landsteiner¹⁶ in 1910 were apparently the first to report on the value of serum in the experimental disease. They were unable to alter the course of the disease in monkeys by intraperitoneal injections of monkey convalescent serum administered on the same day and one and five days after inoculation with virus The same year Flexner and Lewis,¹⁷ however, observed that, if the intracerebral injection of virus is sufficiently small (0.1 c.c. of virus filtrate) and followed within twenty-four hours by convalescent serum intraspinally (2 c.c.), one

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The term therapeutic, as used throughout this paper, refers to the administration of serum any time after experimental inoculation of animals with virus. In other words, the term is not used in the more restricted sense, sometimes employed, of treatment applied after the onset of clinical symptoms.

may in some cases prevent the development of symptoms. Similar results were reported later by Flexner and Amoss¹⁸. Neustaedter and Banzhaf⁹ in limited experimental observations noted that intramuscular injection of immune horse serum twenty-four hours after intraspinal injection of virus served to prevent the development of symptoms. However, serum administered forty-eight hours after inoculation with the virus failed to modify the experimental disease. Weyer, Park, and Banzhaf¹¹ have reported a high percentage of survivors following the use of a concentrated globulin fraction of poliomyelitis immune horse serum administered at varying intervals of time after three daily intranasal instillations of virus. The same year Rhoads,¹⁹ however, using the Park serum in an experiment with three monkeys, obtained inconclusive results. Howitt²⁰ in an extensive experimental study in which convalescent monkey serum was administered by different routes and in varying amounts also obtained what may be regarded as highly inconclusive results.

EXPERIMENTAL WORK

A. Procedures

Macacus rhesus monkeys were employed in the studies here reported. The viruses used were the Aycock and the so called "MV" strains. Both were originally obtained from Dr. Simon Flexner. In the early part of these studies the virus was inoculated by the intracranial route. This route, however, was never regarded by us as altogether satisfactory in a study of this kind. Therefore, before proceeding with the major part of these studies, we carried out an investigation to determine whether the usual incidence of infection by the intranasal route could in some way be appreciably increased. The results of this preliminary work have already been reported (Schultz and Gebhardt²¹). The procedure described has in our hands yielded infection in 90 to 95 per cent of the animals inoculated. The essential features of the procedure are: (1) the use of a mixed virus suspension of high potency (pooled cords from several animals), (2) thorough irrigation of the nasal passages of the animal with a phosphate buffer solution (pH 5) immediately before each instillation of virus, (3) deep ether anesthesia to facilitate carrying out, not only the intranasal irrigations, but also the instillations of virus, (4) three intranasal irrigations and three virus instillations (at about three hour intervals) *on the same day*, (5) virus instillations made high into the nasal vault, at least 0.5 c.c. of a 10 per cent pooled virus suspension being introduced into each nasal passage with each instillation. Unless otherwise stated, this procedure was followed in all inoculations indicated as having been made by the "intranasal route."

The serum employed in these studies consisted for the most part of poliomyelitis immune horse serum exhibiting an unusually high neu-

tralyzing titer in *in vitro* tests. The history of this serum has been described in another paper.¹⁴ It is important to note that this serum in repeated titration studies has exhibited what seems to be the highest virucidal titer of any poliomyelitis immune serum, either of human or animal origin, hitherto reported a fact which should be kept in mind in reviewing the observations reported further on. Poliomyelitis monkey convalescent serum was employed in several of the experiments. The quantity of serum used and the route by which it was administered are indicated in describing the individual experiments.

B Observations

Experiment 1—Six monkeys were injected intracranially with 1.5 c.c. of poliomyelitis convalescent monkey serum 1, 6, 20, 30, 42 and 68 hours, respectively after intracranial inoculation (Apr. 10, 1930) with 0.5 c.c. of a 5 per cent suspension of virus-cord. All the animals developed poliomyelitis in six to ten days following the inoculation of virus. Neither the length of the incubation period nor the severity of the disease bore any relationship to the time interval which elapsed before the serum was administered.

Experiment 2—Two animals were inoculated intracranially (Apr. 25, 1930) with 0.5 c.c. of a 5 per cent suspension of virus-cord. On the first appearance of symptoms such as tremors, five days later, spinal fluid was removed by lumbar puncture and 10 c.c. of monkey convalescent serum was injected slowly into the lateral ventricles, the lumbar puncture needle being left in place to carry off excess fluid. Both animals, nevertheless, developed extensive paralysis.

Experiment 3—Six monkeys were injected intracranially (Mar. 17, 1931) with 1 c.c. each of a 1:1000 virus-cord suspension (aqueous fraction after ether extraction). Four of these animals (398, 399, 400, 401) were given 20 c.c. each of poliomyelitis immune horse serum (Jan. 22, 1931, bleeding¹⁵) by the intramuscular route on the appearance of tremors and excitability (five days after inoculation). All of the treated animals developed as extensive paralysis as the controls (396, 397).

Experiment 4—Two monkeys (796, 797) were inoculated with virus by the intranasal route (Oct. 21, 1932). Six days later and before the appearance of symptoms one of the monkeys (797) was injected with 10 c.c. of immune horse serum (May 3, 1932, bleeding¹⁵) by the intracardial route. Both the control and serum treated animal began to show symptoms of the disease on the eighth day and developed essentially the same degree of paralysis.

Experiment 5—Four monkeys were inoculated with virus by the intranasal route (Nov. 9, 1932). One monkey (830) received no serum, while three were given 10 c.c. each of immune horse serum (May 3, 1932,

bleeding¹⁵) by the intracardial route One monkey (831) received the serum twenty-four hours, one (832) forty-eight hours, and one (833) seventy-two hours after inoculation with virus The control animal developed the disease on the ninth day, the three treated animals on the seventh, eighth, and ninth days No difference in the extent of the paralysis of the control and the serum-treated animals was noted

Experiment 6—Three monkeys were inoculated with virus by the intranasal route (Dec 14, 1932) Twenty-four hours later two of the monkeys (878, 879) were injected subcutaneously with 20 c c each of immune horse serum (May 3, 1932, bleeding¹⁵) One of the animals (879) developed extensive poliomyelitis ten days later and lived for twelve days thereafter, the other (878) remained well The control (869) developed moderately extensive paralysis on the fifteenth day

Experiment 7—Six monkeys were inoculated with virus by the intranasal route (Jan 10, 1933) Two monkeys served as controls (900, 901) Each of the remaining animals (902, 903, 904, 905) were given three injections of 20 c c of immune horse serum (May 3, 1932, bleeding¹⁵) subcutaneously two, four, and six days after the intranasal instillations of virus, each monkey receiving a total of 60 c c of serum All animals in the series developed the disease eight days after inoculation with virus, and no important difference was noted in the extent of the paralysis developed by the serum-treated and the control animals

Experiment 8—Convalescent monkey serum (pooled serum from eleven monkeys) was used in this experiment Six monkeys were inoculated with virus by the intranasal route (Jan 23, 1933) Two monkeys (914, 915) served as controls while the remainder received immune serum by the subcutaneous route Two of the latter (910, 911) received single injections of 20 c c of serum twenty-four hours after virus instillation Both of these developed the disease six days later Two monkeys (912, 913) received three injections of 20 c c each twenty-four, forty-eight, and seventy-two hours after inoculation with virus These developed the disease on the tenth and twelfth days, respectively Both controls (914, 915) came down on the eighth day The two (912, 913), which had received three injections of serum, were not only slower in developing the disease, but also suffered less extensive paralysis and died nine days (912) and fourteen days (913), respectively, after the remainder had succumbed (which was about three days after the appearance of symptoms)

Experiment 9—Three monkeys (988, 989, 990) received pooled monkey convalescent serum (from fourteen monkeys), three monkeys (991, 992, 993) received immune horse serum (July 7, 1933, bleeding¹⁵), and three monkeys (985, 986, 987) served as controls The serum-treated animals received 15 c c of serum by the intracardial

route twenty four, forty eight, and seventy two hours after intranasal inoculation with virus (July 12 1933), each monkey receiving a total of 45 c.c. of serum

All of the serum treated animals developed poliomyelitis eight days after inoculation with virus and presented extensive paralysis within two days after the onset of clinical symptoms. One of the controls (985) remained well, two (986, 987) developed poliomyelitis on the seventh day

Experiment 10—Eight monkeys were given the usual three intranasal instillations of virus on May 13 1934. Twenty four hours after the last instillation four of the monkeys were injected intramuscularly with immune horse serum (pooled bleedings July 7, 1933 and Jan 29 1934¹⁶) in doses of 2 c.c. per kilogram of body weight. These injections were repeated approximately 24, 48, 72, 96, 120 and 144 hours after the intranasal instillations of virus. The results of this experiment are given in Table I

TABLE I

MONKEY	WEIGHT IN KG.	AMOUNT OF SERUM PER DOSE IN C.C.	TOTAL AMOUNT OF SERUM IN C.C.	RESULTS
B-97	2.8	5.6	33.6	Poliomyelitis on 8th day
B-98	3.0	6.0	36.0	Poliomyelitis on 9th day
B-99	3.0	6.0	36.0	Poliomyelitis on 9th day
B-100	3.1	6.2	37.2	Poliomyelitis on 8th day
B-101	--	none	none	Poliomyelitis on 7th day
B-102	--	none	none	Poliomyelitis on 10th day
B-103	--	none	none	Poliomyelitis on 7th day

In view of the fact that the serum employed in this experiment was definitely known from previous tests to possess an exceptionally high virucidal titer and was administered in repeated and in relatively large doses, the first dose having been administered twenty four hours after inoculation of the animals with virus, it would appear that the results of this experiment should be regarded as highly significant. Not only did the serum treated animals develop the disease after approximately the same period of incubation as the controls, but little if any, difference was observed in the extent of the paralysis presented by the two groups—treated and untreated

SUMMARY

The results of ten sets of experiments designed to test the therapeutic value of immune serum in experimental poliomyelitis are summarized in Table II. It will be noted that the observations are surprisingly uniform, despite the fact that the serum was administered in varying quantities by different routes and at varying intervals of time after inoculation of the animals with virus. While several of the

TABLE II
SUMMARY OF RESULTS OBTAINED IN EXPERIMENTS ON THE THERAPEUTIC VALUE OF POLIOMYELITIS IMMUNE SERUM

EXPERIMENT	SOURCE OF IMMUNE SERUM	ROUTE BY WHICH SERUM WAS ADMINISTERED	TOTAL AMOUNT OF SERUM ADMINISTERED (IN CC.)	LENGTH OF TIME AFTER INOCULATION WITH VIRUS	ROUTE BY WHICH ANIMALS WERE INOCULATED WITH VIRUS	CONTROL MONKEYS						SERUM TREATED MONKEYS			
						NUMBER USED IN EXPERIMENT	NUMBER DEVELOPING "POLIO"	AVERAGE INCUBATION PERIOD (DAYS)	NUMBER OF SURVIVORS	SURVIVORS (PER CENT)	NUMBER USED IN EXPERIMENT	NUMBER DEVELOPING "POLIO"	AVERAGE INCUBATION PERIOD (DAYS)	NUMBER OF SURVIVORS	SURVIVORS (PER CENT)
1	Monkey	Intracranially	15	1 to 68 hr	Intracranially						6	6	8	0	0
2	Monkey	Intrathoracically	100	5 days	Intracranially						2	2	5	0	0
3	Horse	Intramuscularly	200	5 days	Intracranially	2	2	8	0	0	4	4	8	0	0
4	Horse	Intracardially	100	6 days	Intranasally	1	1	8	0	0	1	1	8	0	0
5	Horse	Intracardially	100	24, 48, 72 hr	Intranasally	1	1	9	0	0	3	3	8	0	0
6	Horse	Subcutaneously	200	24 hr	Intranasally	1	1	15	0	0	2	1	12	1	50
7	Horse	Subcutaneously	600	2, 4, 6 days	Intranasally	2	2	8	0	0	4	4	8	0	0
8	Monkey	Subcutaneously	200	24 hr	Intranasally	2	2	8	0	0	2	2	6	0	0
			600	24, 48, 72 hr	Intranasally						2	2	11	0	0
9	Monkey Horse	Intracardially	450	24, 48, 72 hr	Intranasally	3	2	7	1	50	3	3	8	0	0
											3	3	8	0	0
10	Horse	Intramuscularly	336 to 372	24, 48, 72, 96, 120 and 144 hr	Intranasally	4	4	8	0	0	4	4	8.5	0	0
Summary of ten experiments						16	15	9-	1	6+	36	35	8+	1	28

earlier experiments (1, 2, 3) cannot be regarded as crucial, later ones, in which the virus was inoculated by the intranasal route, seem to leave little to support the possibility that immune serum does appreciably modify the course of the disease once the virus has become implanted in the nervous tissue. The results of Experiment 8 suggest that the pooled monkey convalescent serum may possibly have exercised some therapeutic effect. It, however, is also quite possible that the difference noted between the treated and control animals rests on some factor other than on the use of serum. It seems particularly noteworthy that the administration of serum as early as twenty-four hours after inoculation of the animals with virus, with one exception only, failed to prevent or modify in any significant degree the course of the disease. An explanation of the inability of immune serum to prevent or modify the propagation of the virus once it is established in the host is presented in the following discussion.

DISCUSSION

Recent studies on poliomyelitis indicate that from the very beginning of the infection the virus is intimately associated with neurons and that once it is established in the nervous system it is propagated largely, if not entirely, along axonal routes. The evidence for this is varied. In 1930 Fairbrother and Hurst²² for example reported experiments in which after inoculation of virus into the brain or on the nasal mucosa the infection apparently advanced along nerve paths from the cerebral cortex to the thalamus from there to the medulla from whence it spreads with almost explosive suddenness to the spinal cord. They noted, moreover, that nerve cell degeneration not only preceded but was often quite independent of inflammatory reactions. Virus was demonstrable in the spinal fluid on rare occasions only. Jungeblut and Spring²³ later in the same year reported the results of an experiment in which the cord of a monkey was transected at the level of the first lumbar vertebra prior to an intracranial inoculation with virus. Nine days following inoculation with virus, typical lesions of poliomyelitis were found in the cervical and thoracic cord while the lumbar cord which is ordinarily most markedly involved in the experimental disease presented a normal appearance. Faher and Gehhardt²⁴ have recently further established the axonal route of dissemination. On sampling different parts of the central nervous system, they found that for periods of less than four days following intranasal inoculation the virus is demonstrable in the olfactory bulb but not elsewhere. By the fifth and sixth days it had spread, apparently entirely by the olfactory tracts and their communications to the hypothalamus where a secondary focus was seemingly established, from whence it spread to the medulla and to the thalamus.

and midbrain. It was first detected in the spinal cord on the seventh day and was present at this time in larger concentrations in the cervical than in the lumbar segments. Certain portions of the central nervous system (e.g., cortex, cerebellum) were never found to contain demonstrable quantities of virus, and some evidence was obtained that it may largely or entirely disappear in areas once involved. In an excellent review of this general subject Faber²⁵ pointed out that clinical observations on man harmonize well with the experimental observations which indicate that the infection is largely limited to individual groups of neurons in the central nervous system.

Further evidence that the virus from the time of the initial invasion propagates itself in very intimate association with nerve cells is afforded by observations recently and simultaneously reported in 1934 by Schultz and Gebhardt²⁶ and Brodie and Elvidge²⁷. This evidence rests on an easily demonstrable fact that after the olfactory tracts have been cut it is no longer possible to infect monkeys with poliomyelitis virus administered by the intranasal route. This simple experiment seems to prove clearly that from the very beginning of the infection the virus is very intimately associated with nerve cells, the initial portal of entry being possibly the terminal hairs of the olfactory nerve. Added to the evidence already presented is the fact that degenerative changes in neurons precede inflammatory reactions in the nearby tissues, furthermore, that intranuclear inclusions and oxychromatic degeneration of the nucleus may be demonstrated in at least a few of the pyramidal cells early in the disease (Covell,²⁸ Hurst,²⁹ Schultz³⁰). Finally, the results of ultrafiltration studies, which point to virus bodies of a magnitude less than 50 mu. (Clifton, Schultz, and Gebhardt³¹), harmonize with the evidence which points to an *intracellular* infection of individual groups of neurons rather than to a more generalized *intercellular* infection.

In the light of this knowledge it is easy to understand the results obtained in the therapeutic studies here reported. If it is correct that in poliomyelitis the virus is confined largely to neurons and is freed from the infected cells only when they are caused to disintegrate, then it is apparent enough why a complex proteinaceous agent such as immune serum, which although it may bathe the exterior of the cell does not reach the virus established within it. This may also explain the results of serum therapy in other filtrable virus diseases—diseases in which a state of *intracellular* rather than *intercellular* parasitism exists.

Whether or not an immune serum may interrupt the passage of poliomyelitis virus from one neuron to another at their synapses, as has been suggested by Faber,²⁵ is a possibility which will command consideration in the presence of any proof that serum is actually of

some therapeutic value. Our results do not indicate that immune serum impedes the progress of the virus at any point along its normal path. It is, of course, possible that in the natural disease in man in which a smaller quantity of virus may be involved and in which the disease tends to progress more slowly, some blocking action may be exercised by serum at the synapsis of neurons. However, the results of recent clinical studies, in which treated and untreated cases have been carefully compared, do not support the possibility that a significant difference exists between the results of serum treatment in the natural and the experimental disease (Park,²² Landon²³)

CONCLUSIONS

Specific immune serum is without demonstrable value in the treatment of experimental poliomyelitis.

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APLASTIC ANEMIA FOLLOWING STOVARSOL (ACETARSONE) THERAPY

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FOR the last eighteen months, stovarsol (acetarsones) has been used exclusively in the treatment of children with syphilis in the clinic of the Cincinnati General Hospital. The results of the therapy have been satisfactory in the group of seventy children who have been treated regularly. Complications of the medication have been few in number and of a very mild nature except in the instance of the patient whose illness is reported here.

CASE REPORT

Family History—The patient's mother died of pneumonia. Her father has been given antisyphilitic treatment. His Kahn test at present is negative. Two brothers of the patient, aged fourteen and sixteen years, respectively, are living and well. One sister, eleven years old, is now receiving antisyphilitic treatment. One sister died at the age of six months, the cause of death being unknown. There is no history of any blood dyscrasia in the family.

Past History—The patient is said to have been a full term, normal infant at birth. She has had measles, mumps, and chickenpox, but no serious illness until the present one. In August, 1932, at the age of six years, she was treated in the Pediatric Clinic of the Cincinnati General Hospital for kerato iritis. The Wassermann reaction was found to be strongly positive and antisyphilitic treatment was instituted on Nov. 2, 1932. Ten doses of a bismuth preparation were administered intramuscularly at weekly intervals, and this was followed by six intravenous injections of 0.1 gm. of nearsphenamine at the same intervals. These treatments were completed on Dec. 14, 1932. Stovarsol was begun on Dec. 28, 1932, in doses corresponding to the Maxwell Glaser¹ method. The dosage was as follows:

- $\frac{1}{4}$ tablet once a day for one week
- $\frac{1}{4}$ tablet 2 times a day for one week
- $\frac{1}{4}$ tablet 3 times a day for one week
- $\frac{1}{4}$ tablet 4 times a day for one week
- $\frac{1}{2}$ tablet 3 times a day for one week
- $\frac{1}{2}$ tablet 4 times a day for one week
- 1 tablet 2 times a day for one week

Each tablet contained 0.25 gm. of stovarsol. The total dosage for the seven week course was fifty six tablets or 14 gm. of the drug. A rest period of one month was allowed between courses in this instance. No other drugs were given during the period of treatment until the patient entered the hospital.

The child received four courses of this medication, completing the last on Sept. 17, 1933.

During the first seven months of antisyphilitic treatment, the child gained 9 pounds, and the only clinical manifestation of syphilis, the kerato iritis, disappeared except for a small scar which remained on the right cornea. The Wassermann and

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Kahn tests continued to be strongly positive. A red blood cell count made during the last course of treatment was 3440 000 cells and the hemoglobin was 64 per cent by the Sahli method. At the child's last visit to the clinic on Sept. 10 1932 it was noted that her skin was rather pale and sallow in appearance but she had no complaints. She did not return until her admission to the hospital on Nov. 14 1933.

Present Illness.—On Nov. 3 1933 the patient, then seven years of age, bruised her right hand in the door of an automobile. The superficial wound was cleaned and dressed, and 1,500 units of tetanus antitoxin were given. A roentgenogram showed no evidence of fracture of the bone. The wound healed well but within a few days a large bluish area appeared in the surrounding skin which became very painful and tender. Simultaneously she became listless and complained of aching of the joints. On the third day following the injury Nov. 6, she had a severe chill which was followed by an elevation of temperature which ranged between 98° F. and 104° F. during the next eight days. The father also noted that the child was very pale. On the seventh day following the injury Nov. 10 a 'gumboil' appeared on the upper left jaw in the region of the premolar teeth, which was incised. On the night of Nov. 14 the child appeared desperately ill and vomited a small amount of watery fluid. She was brought to the pediatrics ward of the Cincinnati General Hospital.

Physical Examination.—At the time of admission to the hospital, she was in a semicomatose condition. She grunted with each expiration, was restless, and seemed acutely ill. There appeared to be hyperesthesia of the whole body surface. Many purpuric areas were noticed on the abdomen, the lower extremities, and especially in the region of the injury to the right hand. The superficial veins stood out prominently on the pale icteric cutaneous surface. The mucous membranes of the mouth and conjunctivae were almost colorless. There was an old scar on the right cornea. Some hemorrhagic areas were present about the gum margins, and on the gum surface of the upper left jaw there was a circular area of necrosis, 3 cm. in diameter, which was surrounded by an area of redness and edema. A similar lesion was noted on the left tonsil which appeared almost gangrenous. The cervical lymph nodes were moderately enlarged. The respiratory rate was 22 per minute. The percussion note over the chest was not impaired, but on auscultation a suppression of breath sounds was noted and a few medium, moist râles were heard over the right chest posteriorly especially in the regions just above and below the spine of the scapula. The heart rate was 92 per minute. The area of cardiac dullness was greatly increased in all directions, the apex beat being diffuse and about 3 cm. to the left of the nipple line. At this point a thrill was palpable. A systolic murmur was audible at the apex, and there was a suggestion of a gallop rhythm. The liver was palpable for a distance of 4 cm. below the costal margin. The superficial and deep reflexes were normal.

Laboratory Findings During First Twenty-Four Hours of Hospitalization.—*Blood*. There were 980 000 red blood cells per cubic millimeter, these being well filled with hemoglobin and practically normal in size and shape. The hemoglobin content was 2.35 gm. per cent, or 17 per cent by the Sahli method. White cell count 2,000. The differential count was lymphocytes, 77 per cent; monocytes, 10 per cent; polymorphonuclear neutrophils, 7 per cent; eosinophils, 1 per cent; transitionals, 3 per cent; undetermined cells, 2 per cent. Platelets were practically absent. The clotting time (capillary tube method) was six and one-half minutes. The bleeding time was greatly prolonged. The blood culture was negative. *Urine Examination*. Acid reaction, acetone three-plus, no sugar, no albumin, no blood by chemical test; microscopic examination negative. *Arsenic Content of the Urine*. 0.02 milligrams per cent of As_2O_3 (an amount which was thought to be of no clinical significance).

An electrocardiogram showed signs of diffuse myocardial disease.

Roentgenologic examination of the long bones, the skull, and pelvis revealed no abnormalities in the intimate structure. On Nov 16, 1933, a roentgenogram of the chest showed an enlarged heart, but the configuration was not pathognomonic of any specific lesion. Rather extensive peribronchial infiltration was present throughout the lungs, suggesting early bronchopneumonia.

Progress—(See Treatment.) On Nov 20, 1933, the sixth day after admission to the hospital, the red cell count was 3,285,000. The differential white cell count was polymorphonuclear neutrophils, 12 per cent, lymphocytes, 79.5 per cent, monocytes, 8 per cent, plasma cells, 0.5 per cent, reticulocytes, 0.1 per cent. Practically no platelets were seen. The red cells were slightly smaller than normal and were well filled with hemoglobin. There was no alteration in the shape of these cells, no stippling, and no nucleated red cells were seen. The polymorphonuclear neutrophils were mostly of the band form, and certain toxic changes were observed, such

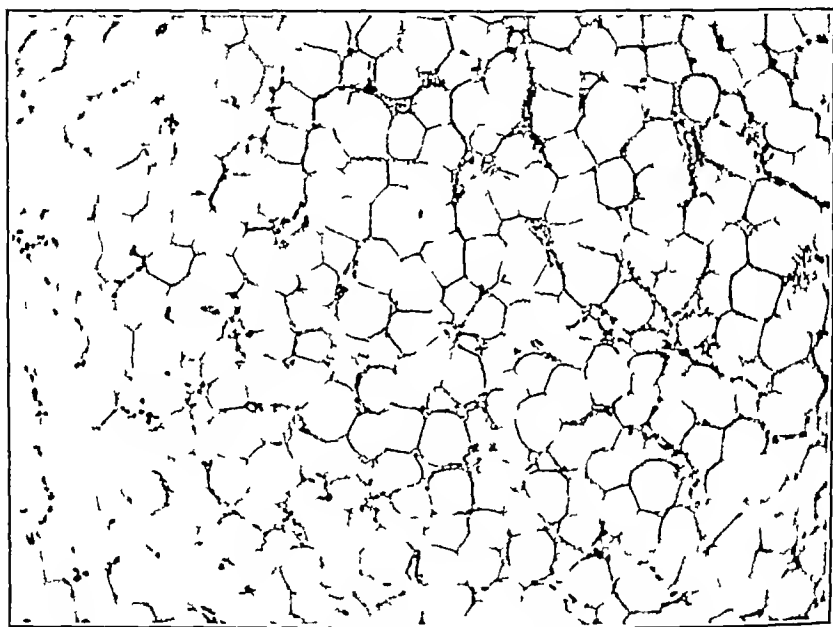


Fig 1—Section of bone marrow of the tibia, Nov 23 1933 (Low magnification.)

as large, deeply staining granules with some vacuolization. The lymphocytes and monocytes were fairly normal in appearance. The blood picture was that of an aplastic anemia.

On Nov 23, 1933, a section of bone marrow was obtained from the tibia and stained with hematoxylin and eosin (paraffin section). On microscopic examination the section revealed a great preponderance of fatty tissue with very few blood cells. The blood cells present were mainly of the lymphocytic series with a marked dearth of cells of the myelocytic series. On examination of the entire section only 2 normoblasts were found, and no megakaryocytes were seen. The only cells of the myelocytic series found were a few degenerate polymorphonuclears. The proportion of cells to fat resembled that of adult bone marrow in this region, but the differential count on the cells present would be abnormal even for adult marrow.

Summary Aplastic bone marrow with striking deficiency in the proportion of cells of the following types: (1) myelocytic, (2) erythrocytic, and (3) megakaryocytic. (Fig 1)

The patient's condition remained critical during the first ten days in the hospital. For a few days she was very drowsy and weak, but slowly she became more alert and rational. The restlessness and hyperesthesia disappeared slowly. After each transfusion the color of the skin and mucous membranes improved. The râles in the left chest had practically disappeared by the tenth day by which time the heart had decreased somewhat in size and the gallop rhythm and thrill had disappeared.

On November 24 the tenth day after admission, a hemorrhage began at the site of the old ulcer on the gum margin. This was checked by the extraction of the upper left premolar and by packing the region. The bleeding time of the patient on this day was one hour. Purpuric spots on the skin were still numerous.

On November 30, the sixteenth day after admission, it was necessary to perform a myringotomy on the left ear drum, and a serosanguineous material drained from this ear for several days. At this time the urine was grossly bloody. This condition lasted for only a few days and was apparently relieved by the transfusions of whole blood.

On Dec. 20 1933, the red cell count was 3,930,000 the white cell count 3,700. The differential count was polymorphonuclear neutrophils, 13 per cent; lymphocytes, 79.5 per cent; monocytes, 8.0 per cent; plasma cells, 0.5 per cent; reticulocytes, 0.1 per cent. Practically no platelets were seen. The red blood cells seemed smaller than normal. There was no polikilocytosis, very little anisocytosis, and the cells appeared to be well filled with hemoglobin. No stippled or nucleated red cells were seen. The polymorphonuclears were mostly of the band form and showed the same toxic changes as on the previous examination. The absence of platelets and the low percentage of polymorphonuclears with marked toxic changes in them demonstrated that the bone marrow was still under the influence of some severe depression.

On Feb. 5 1934, the red cell count was 3,600,000 the white cell count, 6,700. The differential count was polymorphonuclear neutrophils, 27.5 per cent; lymphocytes, 68 per cent; monocytes, 4.5 per cent. The platelets had increased in number since the previous examination but were still below normal. The polymorphonuclears did not show much toxic degeneration. The red blood cells were normal in size, and the appearance of the hemoglobin indicated definite signs of regeneration since polychromatophilia was a prominent feature and normoblasts were seen. The whole picture indicated marked improvement.

On Feb. 7, 1934 she was discharged from the hospital.

Outcome of the Case—The patient returned to the clinic twice for observation. On each occasion there was a great improvement in her color and general health. The heart had returned to its normal size. The only syphilitic manifestation was the old corneal scar on the left eye. The Wassermann, Kahn and Meinicke reactions of the blood were negative on Apr. 25 1934, but the Kahn was two-plus on June 20 1934.

On Feb. 21 1934 the red cell count was 3,800,000, the hemoglobin, 91 per cent. The differential count was polymorphonuclear neutrophils, 20 per cent; lymphocytes, 73 per cent; monocytes, 6.5 per cent; plasma cells, 0.5 per cent. The reticulocyte count was 2.5 per cent. The blood picture was about the same as upon previous examination.

On Apr. 25, 1934 the red blood count was 4,320,000 the hemoglobin, 79 per cent the white cell count, 9,350. The differential count was polymorphonuclear neutrophils, 55.5 per cent; lymphocytes, 40 per cent; monocytes, 2.5 per cent; plasma cells, 2.0 per cent. Platelets were present in normal numbers. The general condition of the blood had greatly improved since the last examination.

Treatment.—A summary of certain specific therapeutic measures employed during the patient's stay in the hospital is as follows:

Nov 14, 1933	Blood transfusion, 180 c c
Nov 15, 1933	Sodium thiosulphate, 15 grains. Blood transfusion, 300 c.c, 150 c.c , glucose and 10 c.c. liver extract intravenously
Nov 16, 1933	Sodium thiosulphate, 15 grains, blood transfusion, 250 c c
Nov 19, 1933	Blood transfusion, 300 c c , sodium thiosulphate, 11 grains
Nov 25, 1933	Blood transfusion, 250 c.c , liver extract, 23 c c

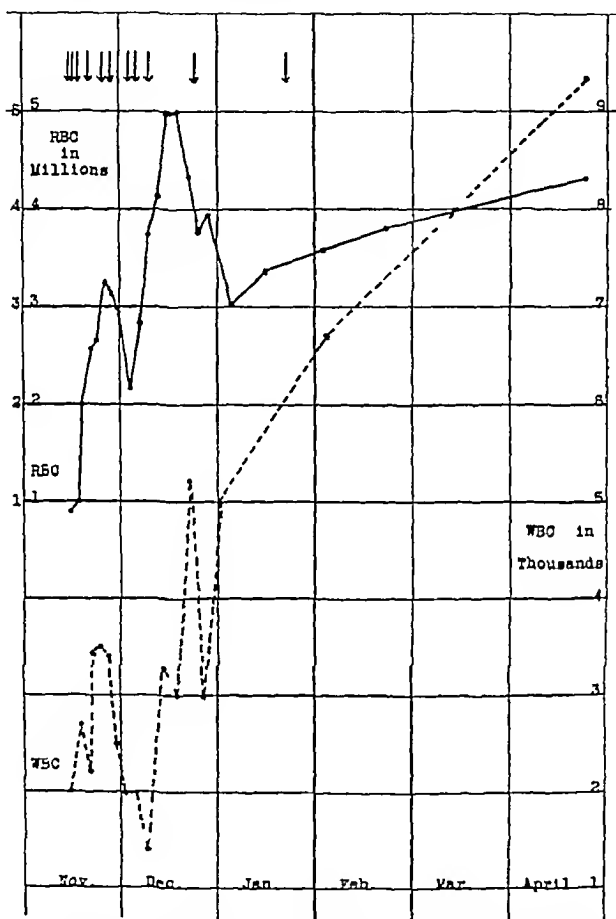


Chart 1—Illustrating the course of the red and white counts during the illness. The arrows at the top indicate blood transfusions.

Nov 27, 1933	Blood transfusion, 180 c c.
Dec 3, 1933	Blood transfusion, 500 c c.
Dec 4, 1933	Pentnucleotide, 10 c.c intramuscularly
Dec 5, 1933	Blood transfusion, 400 c.c , pentnucleotide, 10 c c intramuscularly
Dec 7, 1933	Pentnucleotide, 10 c.c intramuscularly
Dec 9, 1933	Blood transfusion, 400 c c.
Dec. 6, 1933	Addition of vitamin concentrates, liver extract, and iron compounds to diet

Dec. 14, 1933	Extra calcium added to diet in the form of di calcium phosphate and calcium gluconate
Dec. 23, 1933	Blood transfusion, 400 c.c.
Jan. 23, 1934	Blood transfusion, 400 c.c.

A graphic representation of the course of the red and white blood cell counts may be seen in Chart 1.

SUMMARY

The patient was a seven year-old girl with congenital syphilis who suddenly developed a severe form of aplastic anemia apparently due to the arsenicals used in the treatment. The antisyphilitic treatment had extended over a period of ten months and had consisted of ten injections of a bismuth preparation, six injections of 0.1 gm. of neoarsphenamine (total of 0.6 gm.) and four courses of stovarsol (total of 56 gm.) Treatment included eleven blood transfusions, and the child gradually improved during the next four months making a complete recovery.

COMMENT

To the best of our knowledge, no previous reports of aplastic anemia following the use of stovarsol have appeared in the medical literature.

Agranulocytosis was observed in a patient treated with stovarsol by W. Habermeld and M. Rudolph.² Agranulocytosis and purpura hemorrhagica occurred in a patient reported by E. Benhamou, P. Temin, and R. Lofrani.³

The rarity of blood dyscrasias following the use of other antisyphilitic arsenicals (arsphenamine, neoarsphenamine, sulpharsphenamine, tryparamide, etc.) was illustrated by a review of the literature made by F. P. McCarthy and R. Wilson⁴ who found reports of only thirty-four cases of aplastic anemia with a mortality rate of 83 per cent, twelve of thrombocytopenia, seven of thrombocytopenia and granulocytopenia, and twelve of agranulocytosis and granulocytopenia.

For assistance in the examination of the blood smears, we are indebted to Dr. Murray Rich, of the medical department, for the determination of the arsenic content of the patient's tissues, to Dr. Robert Kehoe of the Kettering Laboratory, department of physiology, and for the examinations of the bone marrow sections to Dr. Pearl Zeek, of the department of pathology, College of Medicine of the University of Cincinnati.

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MASKED MASTOIDITIS

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MASKED mastoiditis is commonly defined as a mastoid infection occurring in infants and is characterized by the symptoms of a gastrointestinal intoxication and otitis media. Its existence, however, is still controversial. Hartmann,¹ Marriott,² Alden and Lyman,³ Floyd,⁴ Lyman,⁵ Odoneal,⁶ and Pease⁷ observed that mastoiditis may be the primary infection when it occurs in association with infantile gastroenteritis. On the other hand, Maybaum,⁸ Johnston and his coworkers,⁹ and Wishart¹⁰ were unable to establish any relationship between intestinal intoxication and mastoiditis in infancy.

The evidence of Johnston and his associates against the existence of masked mastoiditis consisted of bacteria of the colon-paratyphoid-dysentery group of bacilli, which they isolated from the stools in acute intestinal intoxication. Wishart,¹⁰ working with the same school, submitted the question to a practical test. Bilateral mastoid antrotomy was performed on thirteen severely toxic infants. He failed to influence the course of the toxemia, and only one infant recovered. He concluded that masked mastoiditis was not the cause of the intestinal disturbance.

The large number of cases of otitis media with gastroenteritis available at the Kings County Hospital offered an opportunity for several clinical and pathologic observations. They are presented as evidence in favor of the clinical entity of masked mastoiditis.

DESCRIPTION OF CASES

One hundred nineteen infants with gastroenteritis and otitis media came under observation from 1930 to 1934. These patients were admitted from the free dispensary whose clientele is composed largely of underweight, undernourished infants. Their ages varied from a few weeks to thirteen months. Approximately one-third were females, and about one-fifth were negro infants.

CLINICAL COURSE AND SYMPTOMS

The clinical course in our patients revealed three stages. In stage 1 the nutritional progress of the infant was suddenly halted by fever. Examination revealed otitis media. Following myringotomy or spontaneous perforation of the eardrum, fever subsided, and the few ounce loss was frequently regained. The ear drainage persisted. Stage 2 was characterized by occasional vomiting, an increase in the number of

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stools, which became slightly watery, a gradual loss of weight, and a low grade fever. Stage 3 set in from several days to two or three weeks following the opening of the eardrum. The onset was notably tempestuous. The temperature rose acutely from three to five degrees and simultaneously the weight fell 8 to 30 ounces. The infant now presented the common picture of acute intestinal intoxication. Diarrhea and vomiting became severe, dehydration was rapid, weight fell in spite of supportive therapy, anorexia was common, the infant was apathetic and rarely cried. Unoperated or late operated cases usually proceeded to athrepsia, cachexia, and death.

Two variations from the customary clinical course were noted. In some instances stage 1 was rapidly followed by stage 3. In another small group a milder course was observed in whom dietetic measures proved unavailing, whereas mastoid antrotomy resulted in rapid recovery.

It is our opinion that the mastoid infection set in coincident with stage 2, but the failure of the infants' resistance precipitated the profound toxemia of stage 3.

DIAGNOSIS

The diagnosis of masked mastoiditis depended entirely upon the clinical picture described. The classical symptoms and signs of mastoiditis were rarely present. The x ray examination was not relied upon since many proved mastoid infections produced normal roentgenograms. The swelling of the posterior superior canal described by Lyman³ frequently occurred too late to be of value.

ANALYSIS OF CASES

A. Analysis of Surgically Treated Cases. Fifty patients were submitted to operation. This consisted of bilateral mastoid antrotomy and in a few instances of unilateral antrotomy. At operation pus, granulations, and sequestrums of bone were found. There were twenty three recoveries, a mortality of 54 per cent.

These cases were studied to determine the conditions that influence the prognosis. One factor appeared to exert a striking effect upon the mortality. Calculating the percentage of loss of weight, determined from the onset of the ear infection to the day of operation, it was evident that an acute loss of weight of more than 10 per cent frequently foreshadowed a fatal outcome for the patient. Upon this basis, further analysis of the fifty cases submitted to operation disclosed that of twenty six patients who had lost less than 10 per cent of weight at the time of operation, there were twenty-one recoveries, a 19 per cent mortality, while of twenty four patients who had lost more than 10 per cent of weight, there were only two recoveries, a 92 per cent mortality.

B. Analysis of Medically Treated Cases. Sixty nine patients presented the syndrome described but were not operated upon. Only ten infants recovered, a mortality of 85.5 per cent. These patients were

treated with transfusions, dietetic changes, hypodermoclysis and phlebotomy. The mortality of this group and that of the group operated upon after a 10 per cent loss of weight appeared significantly alike.

ANALYSIS OF AUTOPSIES

There were twenty-five autopsies in this series—eleven from the surgically treated group, and fourteen from the medically treated group. In the former the operative diagnosis was verified. An acute inflammation of the meninges was present in one patient. In the medically treated group otitis media and mastoiditis were demonstrated in all. In addition, osteomyelitis of the petrous bone was discovered in two patients and a sinus thrombosis, in one.

Many otologists are under the impression that the antrum of an infant normally contains debris and cloudy material. On this basis they are frequently skeptical of the diagnosis of mastoiditis made at the operating or autopsy table. Wishart¹⁰ made a controlled study of the infant antrum at autopsy. He observed that the mastoid antrums of infants at autopsy were as a rule healthy and that the presence of infection or accumulations was antemortem in origin. Our own observations confirm these conclusions.

TREATMENT

The operation consisted of bilateral mastoid antrotomy and drainage performed, in most instances, under local anesthesia. The simplicity of the procedure offered practically no operative risk. Rabbiner¹¹ reported nine cases of masked mastoiditis. He concluded that unilateral antrotomy in the presence of bilateral otitis media proved inadequate. Our experience coincides with this view, for it is possible that there may be a localized pocketing of pus on the other side.

Supportive measures were used before and after operation. It served to increase and elevate the patient's resistance until the infection subsided.

Many physicians unfortunately believe that operation is indicated only if the patient has the classical signs of mastoiditis or that operation is not necessarily urgent and should be postponed as long as possible. Such temporizing seems to carry a high mortality rate and is contrary to the general surgical principle that an operative procedure offers less risk before the infant has become cachectic and athreptic.

The otologist and pediatrician should realize that this disease represents an emergency comparable to an acute appendicitis. Surgical intervention should be instituted before there is a severe loss of weight. It is only in this way that the mortality can be appreciably diminished.

CONCLUSIONS AND SUMMARY

Undernourished, underweight infants were found especially susceptible to masked mastoiditis.

The disease seemed to follow a distinct clinical course and was manifested by otitis media and gastroenteritis.

The prognosis depended upon early bilateral mastoid antrotomy, as evidenced by our mortality statistics.

The mortality in the medically treated group was 85.5 per cent.

Bilateral mastoid antrotomy carried a mortality of 5.4 per cent.

Operation performed before there was an acute loss of more than 10 per cent of the body weight carried only a 1.9 per cent mortality.

Operation performed after there was an acute loss of more than 10 per cent of the body weight carried a 92 per cent mortality.

The response to early operation evidenced by the rapid regression of the intestinal symptoms and prompt response to supportive therapy warranted the diagnosis and defended the treatment.

We are indebted to Dr. George Brockway, attending in pediatrics, for helpful advice and guidance in this study.

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ACUTE LYMPHATIC LEUCEMIA IN CHILDHOOD

A STUDY OF SIXTY CASES WITH ESPECIAL REFERENCE TO THE CYTOLOGIC CHARACTERISTICS OF THE BLOOD

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ACUTE lymphatic leucemia, although a relatively uncommon disease, occurs not infrequently in childhood. Warren¹ in 1928 gathered reports of 500 cases from the literature, beginning with the first description of the acute form of lymphatic leucemia by Friedreich² in 1857. Sixty cases of acute lymphatic leucemia among children have been observed at the Mayo Clinic between the years 1921 and 1933, and from them an analysis has been made of the clinical and hematologic findings.

In more than half of the sixty cases the patient was in the first four years of life, the youngest being eight and a half months of age and the oldest, thirteen and a half years. Males predominated over females in the ratio of 36:24. This predominance was especially marked during the first four years of life when males outnumbered females two to one. The predominance of the disease among males has generally been recognized by Warren, Waid,³ and Ordway.⁴ The tendency for the condition to affect children in the age group from one to four years has been mentioned by Ramsey,⁵ who found in his series of 100 cases among children that twice as many children in this age group were affected as were those in the group between the ages of four and eight years. The incidence of the disease in cases included in this paper is given in Chart 1.

The clinical picture of the disease is so generally known that little need be said about it here. The onset of the condition was often insidious and began with an infection of the upper portion of the respiratory tract in more than half of the cases. Infections of the respiratory tract are not generally recognized as precursors of acute leucemia, and the frequency of their occurrence in the present series is to be emphasized. Warren has drawn attention to this and classifies the prodromal symptoms into three groups: (1) sore throats and enlarged tonsils, (2) ulcerative stomatitis, and (3) "colds that hang on."

Pallor and enlargement of lymph nodes, usually of those of the cervical group, were the most frequent initial symptoms, and they occurred in fifteen and fourteen cases, respectively. The next most common initial symptoms were cachectic in nature and occurred in ten cases, these included weakness in four, listlessness in three, irritability in one, and restlessness at night in two. Less frequent were pains in the extremities and hemorrhages, which occurred in six and three cases, respectively.

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The relation of subjective symptoms appearing first as initial symptoms and then later after the onset of leucemia was as follows fever and night sweats were initial symptoms in two cases and appeared after the onset of leucemia in twenty four, weakness was initially present in four cases and later in nineteen anorexia occurred initially in none but later in eighteen listlessness occurred initially in three and later in twelve irritability initially in one and later in twelve difficult breathing initially in none but later in thirteen painful extremities initially in three and later in nine restlessness at night initially in two and later in eight, and abdominal pains initially in two and later in five

The relation of objective symptoms appearing first as initial symptoms and then later after the onset of leucemia was as follows enlarged lymph nodes were initial symptoms in fourteen cases and appeared later in forty-one an enlarged spleen occurred initially in none but later in fifty four hemorrhages occurred initially in three and later in forty



Chart 1.—Age and sex incidence of acute lymphatic leucemia.

seven pallor initially in fifteen and later in thirty five and an enlarged liver initially in none but later in forty nine

It is often possible by examination of the blood to make a diagnosis of acute lymphatic leucemia in the presence of indefinite complaints, such as weakness, listlessness, anorexia and irritability, before the appearance of the more classical symptoms of enlargement of the liver and spleen and hemorrhages in the skin and mucous membranes. Ordinarily acute lymphatic leucemia in childhood runs a course lasting about ten weeks, and the diagnosis in most instances is not made until the disease has run more than half its course. Routine morphologic studies of the blood among patients with weakness pallor, cachexia unexplained fever, and enlargement of the lymph nodes will frequently establish the diagnosis early in the course of the disease.

Because of the relatively greater incidence of acute lymphatic leucemia in early childhood at the time when the lymphatic structures of the body attain their greatest development and when the blood normally

contains a larger proportion of lymphocytes, the diagnosis of leucemia of the acute lymphatic type at times becomes exceedingly difficult. As the clinical features are not always characteristic, careful examination of the blood usually will assist one in making the diagnosis. The results of such studies of the blood in these sixty cases of acute lymphatic leucemia are reported here.

It might be well to say a word about the normal blood picture in infancy and childhood as it appears in the standard works on the subject.^{6, 7, 8} At birth, values for hemoglobin, erythrocytes, and leucocytes are all above the normal figures for adults. This is attributed to the overactivity of the bone marrow which carries over from fetal life. By the Sahli method the hemoglobin content of the blood averages more than 100 per cent, until the age of two weeks, falls rapidly to 75 per cent at six months and stays there for the remainder of the first year. After this period, there is a gradual rise to an adult value of from 85 to 100 per cent, which is attained at sixteen years of age.

The erythrocyte count⁸ at birth varies from 5,000,000 to 9,000,000 per cubic millimeter of blood, this value falls to 5,000,000 at the end of two weeks and then decreases gradually to between 4,000,000 and 5,000,000 per cubic millimeter at six months of age. From then on there is a gradual increase to the adult value of 5,000,000 per cubic millimeter at fifteen or sixteen years of age.

Leucocytes, according to Lippman,⁷ average 16,000 per cubic millimeter of blood at birth, rise sharply to 22,000 at twelve hours, then fall rapidly to from 7,000 to 10,000 per cubic millimeter at five days. Washburn's⁹ recent work emphasizes the marked variability of leucocyte counts among normal, healthy infants. There is a gradual rise to 10,000 per cubic millimeter which is maintained during the remainder of the first year, this is followed by a slight fall in the total number of leucocytes until the fourth year when an average of 9,000 per cubic millimeter is reached, in accordance with the figures of Peilin.¹⁰ The number remains constant until the eighth year, then decreases gradually to adult figures at the sixteenth year. There is a normal physiologic variation in the total leucocyte count which is marked by an increase that takes place between 2 and 4 P.M. and a similar increase that takes place between these same hours in the early morning. This has been shown by Sabin,¹¹ as well as by Shaw,¹² to be due to an increase in neutrophils in the peripheral circulation. As most of the blood counts in the present cases were done in the morning, variations due to physiologic changes largely are eliminated.

The differential leucocyte count indicates that the percentage of neutrophils varies inversely with that of the lymphocytes.⁶ The neutrophils compose from 60 to 70 per cent of the total number of leucocytes at birth, decrease to a number equaling the lymphocytes at forty-eight hours, and continue to decrease to 30 per cent at the end of the

first week of life. At the age of five years, the percentage of neutrophils again has risen to equal that of the lymphocytes and from then on always exceeds the latter. The age at which the adult neutrophilic lymphocyte ratio is reached is sixteen years. The lability of neutrophils is notable. Their percentage of the total leucocyte count may vary from 38 to 61 in six hours.⁷ The monocytes range from 7 to 10 per cent during the first year of life, but they thereafter decrease in number. The eosinophiles may comprise 6 per cent of the total number of leucocytes from the ages of three to five years but are fewer after that time. The platelet count is variable: if low at birth, it tends to rise and vice versa. The usual number of platelets in the blood during infancy and childhood is between 200 000 and 300 000 per cubic millimeter by the direct method using sodium citrate as the diluent and no stain.¹¹ The numerous variations in the methods of counting platelets in which normal values range from 200 000 to 700 000 per cubic millimeter depending on the method employed make such counts worthless unless the method used and its normal value are understood.

Immaturity in the erythrocytes and a shift to the left indicative of immaturity in the leucocytes are normally present the first few days after birth. Normoblasts are seen in decreasing numbers up to five days of age. Polychromatophilia and anisocytosis are normally found during the first two weeks of life. Metamyelocytes and a few myelocytes occur normally during the first week after birth. Immaturity of the leucocytes is readily produced by infection in infancy due to the lability of the bone marrow at this age. It is this factor which at times makes the diagnosis of leucemia among young children extremely difficult.

STUDIES OF THE BLOOD IN ACUTE LYMPHATIC LEUCEMIA

Secondary anemia was the rule, with low values for hemoglobin and for erythrocytes. Few other conditions in childhood present such a picture of severe and long-standing secondary anemia. In most cases, the concentration of hemoglobin was about 30 per cent by the Dare method and erythrocytes numbered from 1 000 000 to 2 000 000 per cubic millimeter of blood. The presence of normoblasts, polychromatophilia and anisocytosis usually was encountered. Absence of these features indicated a lack of regeneration of the erythrocytes and an aplastic type of blood picture. This is not uncommonly found in the terminal stage of acute leucemia.

Reviewing the leucocyte counts in this series of sixty cases of acute lymphatic leucemia using a median value of 10 000 per cubic millimeter as the dividing line between a low and high leucocyte count, thirty-eight patients had counts whose median was greater than 10 000 per c.mm. The highest count in the group was 1,580 000 leucocytes per cubic millimeter. Four patients had leucocyte counts that ranged constantly near the

median of 10,000 per cubic millimeter. Eighteen had counts whose median value was less than this. Of fourteen selected patients studied over a long period, all but one had a median leucocyte value less than 10,000 per cubic millimeter (Table I). In only two cases did these values exceed 5,000 per cubic millimeter.

TABLE I

SEVERE SECONDARY ANEMIA AND LEUCOPENIA. MEDIAN VALUES IN FOURTEEN CASES OF ACUTE LYMPHATIC LEUCEMIA STUDIED OVER LONG PERIODS

CASE	HEMOGLOBIN, PER CENT	ERYTHROCYTES	LEUCOCYTES	LEUCOCYTE COUNTS TOTAL NUMBER	LEUCOCYTE COUNTS HIGHER THAN 10,000 PER C MM
1	35	2,220,000	4,900	29	6
2	44	3,370,000	4,900	33	1
3	40	2,520,000	3,600	17	3
4	40	2,560,000	4,650	57	13
5	25	1,610,000	5,000	11	0
6	41	2,630,000	4,800	32	11
7	47	2,770,000	8,900	14	5
8	34	2,590,000	6,100	18	1
9	40	2,080,000	3,400	21	0
10	30	1,800,000	4,200	18	7
11	33	2,310,000	4,800	18	0
12	23	1,530,000	3,350	14	0
13	37	2,820,000	28,400	44	34*
14	26	1,660,000	4,100	14	0
				340	81

*If Case 13 is omitted only 16 per cent of all the leucocyte counts in the remaining thirteen cases rose above 10,000 per cubic millimeter. In only two instances were the median leucocyte counts higher than 5,000.

It is to be noted that approximately a third of the sixty patients had a leucopenic phase at some time during the course of the condition. Eleven of these were followed for periods varying from three weeks to three and a half months. Daily counts were made in most cases in which it was demonstrated that the leucopenic phase was not transitory. In some cases leucocytosis which could not be attributed to infection was noted. It is possible that in some cases the disease may run its entire course with no leucocyte count above the normal range. It must also be stated that the cases characterized by normal or subnormal leucocyte values were not those in which patients were most actively treated with radiotherapy. They maintained a low leucocyte count for long intervals during which no treatment was given. The clinical aspect in these cases did not vary from that in the more usual type of case in which the leucocyte count was high. The presence of definitely immature leucocytes in the peripheral circulation established the diagnosis of acute lymphatic leucemia in every case when followed for a sufficiently long time. It seems worthy of repetition that the conception of acute lymphatic leucemia as a disease typified by an increase in the leucocyte count is erroneous, since a third of our cases failed to bear this out. A

physician must be on his guard not to pass over those cases in which the leucocyte counts are low or which present other features of leucemia. This may be avoided by repeated examination of the blood smears for immaturity in the leucocytes.

MORPHOLOGIC CHARACTERISTICS OF THE LEUCOCYTES IN ACUTE LYMPHATIC LEUCEMIA

The morphologic characteristics of the leucocytes were reviewed in six cases in which patients were followed for as long as three months, the blood smears were taken at short intervals and in most cases daily. Immaturity of the lymphocytes back to the stem cell could be demonstrated in every case. Since immature cells were not present in every smear, repeated examinations of the blood, taken at frequent intervals often were necessary to discover their presence. In two cases it was noted that the type cell was approximately 12 microns in diameter, with a bluish rim of cytoplasm so small as to appear absent in some instances. On casual observation these cells could easily be mistaken for normal lymphocytes, but more careful inspection of the nucleus revealed that the chromatin was arranged in fine strands sharply demarcated from the parachromatin. Nucleoli were frequently seen in these nuclei. Occasionally an immature lymphocyte was seen with a stippled appearance of the nuclear chromatin in contrast to the more usual type cell with the stringlike arrangement of chromatin. The persistence of such immature cells in the blood in spite of their small size established the diagnosis of acute lymphatic leucemia.

By studying the blood smears for a long time in almost every case, it was possible to demonstrate the presence of lymphocytes with indented, notched, cleft, bisected or lobulated nuclei. The more immature the cell, the greater the tendency to irregularity of the nuclear border. The outline of these cells is well illustrated in Fig. 1. In all these primitive cells the fine sieve-like arrangement of chromatin distinct from the parachromatin and the presence of nucleoli established the immaturity of the cell. The amount of cytoplasm of these cells was small; the cytoplasm was bluish gray with a clear perinuclear zone, and it contained azure granules that were very fine in all but one case. Such cells are probably to be classed as Rieder forms and have been well depicted in the work of Pappenheim¹⁴ Downey¹⁵ and more recently of Gittins.¹⁶ The frequency with which this type of immature cell was encountered and its rather striking appearance seem worthy of emphasis.

Plasma cells were often found containing very dark cytoplasm with a round or oval nucleus, usually eccentric in position and filled with heavy dark chromatin strands that almost completely covered the parachromatin. These cells were not a constant finding in any case in which they appeared and their significance cannot be stated.

In several cases unusually small lymphocytes and neutrophils with mature nuclei were noted, ranging from 5 to 7 microns in diameter. The granules in the cytoplasm of these neutrophils were somewhat coarser

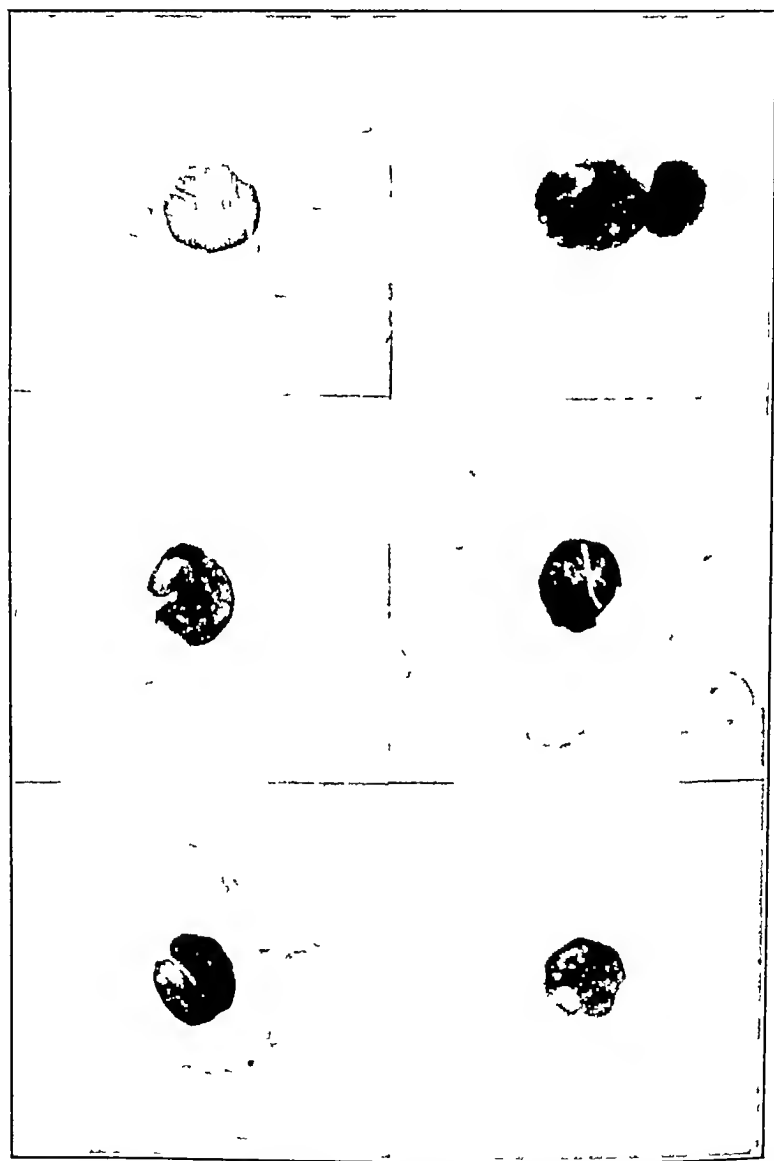


Fig 1—Immature lymphocytes with nuclear indentations seen in acute lymphatic leucemia. Variations in nuclear contour and narrow band of cytoplasm about nuclei may be seen ($\times 1000$)

than normal and their nuclei rather pyknotic. Such cells were taken as evidence of unusual activity of the bone marrow which poured out cells into the blood stream before they had ripened to mature sizes.

A shift to the left and the appearance of toxic changes in the polymorphonuclear neutrophils were not uncommon. Immaturity often occurred in both myeloid and lymphatic series at alternating periods, so that it was necessary to follow the blood smears over extended periods to determine in which series the immaturity predominated. The lability of the bone marrow in childhood may account for this finding. A lessened degree of immaturity appeared to parallel the subjective improvement of the patient.

The toxic neutrophil was frequently seen and was characterized by the dark, pyknotic nature of the nuclear chromatin which was irregular in distribution. The neutrophilic granules in the cytoplasm varied greatly in size, shape and in staining intensity, tending to be coarser than usual and more angular than round. Vacuoles not uncommonly occurred in the cytoplasm and the cell border was often irregular and ill defined. The immature lymphocytes showed vacuolization and fragmentation very frequently.

The erythrocytes exhibited the usual picture of secondary anemia with anisocytosis, polychromatophilia and the presence of reticulocytes and normoblasts, indicating good regeneration of the erythrocytes. An aplastic blood picture was not encountered in the cases in this series.

The platelet counts by the citrate method were uniformly low in all instances in which they were made. This finding has been noted in the literature and in the chronic form of the disease has been used by some as a differential point to distinguish lymphatic leukemia from the myelogenous type, since the latter is usually accompanied by an increase in platelets. It has been stated by Minot and Buckman¹⁷ that an increase in the blood platelets is indicative of improvement.

EFFECTS OF BLOOD TRANSFUSION

After transfusion of blood the values for hemoglobin rose rapidly, the erythrocyte count less rapidly. Whereas the value for hemoglobin in some cases rose the day following transfusion the erythrocyte count did not attain its maximal increase until the third day after this procedure. The effects of transfusion on the leucocytes were threefold: first the total count tended to return to normal, that is, if it had been high there was a decrease and if low, a rise. The maximal effect was noted from three to five days after transfusion. Second the degree of immaturity of the leucocytes became less, and third the normal ratio of neutrophils to lymphocytes was restored. Subjective improvement was the usual accompaniment of these changes.

EFFECT OF RADIUM AND ROENTGEN THERAPY

Treatment with radium and roentgen rays causes a more rapid and pronounced fall in the number of leucocytes in the circulating blood when their numbers are greater than normal. Minot and Spurling¹⁸

found an elevation of the leucocyte count and of the number of neutrophiles in the first twenty-four hours following treatment with roentgen rays of a leucemic patient. Following this, there was a decrease in the leucocyte count and in the neutrophile count which reached their lowest values six days after treatment. A slight decrease in values for hemoglobin and erythrocytes follows the use of radiotherapy. The lymphocytes are reduced in number more rapidly than are the neutrophiles, so that a relative polymorphonuclear neutrophile leucocytosis results. Radiotherapy has a more lasting effect than transfusion but is less marked with each repetition. Following this procedure, too, a sense of well-being is restored.

EFFECT OF INTERCURRENT INFECTIONS

Intercurrent infections had no constant effect on the leucocyte level, nor was there an increase in the number of neutrophiles in the four cases in which infection occurred and in which blood smears were studied. In two cases there was a rise in the total leucocyte count, but no accompanying increase in neutrophiles. In one case a definite increase in immaturity of the leucocytes occurred as a result of intercurrent infection.

TERMINAL LEUCOCYTE COUNTS

The leucocyte counts at death were followed in sixteen cases in which records were made within the last three days of life. In only one case was there a terminal rise, which may be explained as the last burst of activity of the overtaxed bone marrow. The other fifteen patients had leucocyte counts which remained at their previous level or showed a terminal decrease. In eight cases transfusions or radiotherapy within the last three days of life might be considered causative factors in the terminal fall in the leucocyte counts where previous levels had been elevated. There was no tendency noted toward terminal increase in leucocytes, in seven cases in which leucocyte counts were low, with the possible exception of the first case cited. In fact, the converse was more generally true, and it indicated exhaustion of the hematopoietic depots as death approached.

SUMMARY

Acute lymphatic leucemia, although rare, is a disease that occurs not infrequently in childhood, especially in the first four years of life. The condition predominates among males in all age groups, especially affecting those in the youngest age group. In approximately a third of the cases, the leucocyte count is less than 10,000 per cubic millimeter of blood. A high leucocyte count is not necessary to make the diagnosis. Marked secondary anemia usually is present. The most reliable diagnostic finding is the repeated observation of immaturity in the lymphocytes back to the stem cell. Morphologic findings of frequent occurrence

in the blood smears in cases of acute lymphatic leucemia are stem cells of unusually small diameter, Rieder forms, plasma cells and toxic neutrophils. The effects of transfusion, radiotherapy, and intercurrent infection on the blood are noted. The terminal leucocyte counts tend to be low. It would be possible to make the diagnosis earlier in more cases if routine morphologic examinations of the blood were made.

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LOW CALCIUM TETANY OF THE NEWBORN

REVIEW OF THE RECENT LITERATURE AND REPORT OF ANOTHER PROVED CASE

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CASES of low calcium tetany in the newborn are being reported in the literature with increasing frequency. Recently, the author¹ described a case of tetany of the newborn which he had observed over a year ago. Hyperpyrexia had been present from birth, and twitches and convulsions had appeared on the thirteenth and seventeenth days of life. The blood calcium concentration had been 7.4 mg. In this report mention was made of only three prior reports in the literature of proved cases of low calcium tetany occurring within the first three weeks of life (Shannon's third case,² Bass and Karelitz' first case,³ and Maslow's third case⁴). Unfortunately, reports by Nesbit⁵ and Sinecock⁶ had been overlooked. Nevertheless, of the six cases comprising Nesbit's report, only the first case had a sufficiently lowered calcium concentration (8 mg.) to be included in the above list of proved cases of low calcium tetany of the newborn. In Sinecock's two cases the blood calcium concentrations were 7.0 and 6.0 mg., respectively, in the presence of marked hypertonia of the muscles of the extremities, positive Chvostek phenomena, and a 4 milliamperere cathodal opening contraction to the galvanic current. In addition, in his second case projectile vomiting and hyperpyrexia occurred.

Several other reports have appeared in the literature since the preparation of the author's first paper. In June, 1933, Small⁷ reported the onset of twitchings of the face and of the extremities in a nine-day-old infant with a convulsive seizure on the eleventh day. On the sixteenth day of life, a week after the onset of symptoms, the calcium content of the blood was determined for the first time and found to be 5.6 mg. per hundred cubic centimeters of serum. Calcium chloride was given orally with resultant cure. The Chvostek and Trousseau phenomena were negative, and no laryngospasm was noted.

In September, 1933, Guild⁸ described the appearance in a two-day-old infant of spastic seizures accompanied by laryngeal stridor, cyanosis, and positive Chvostek and peroneal phenomena. Although the spinal fluid calcium content was found to be 3.9 mg. per cent, the blood calcium content was not determined. Since the spinal fluid calcium is approximately 45 per cent of the blood calcium, the corresponding blood calcium would probably be 9 mg. Therefore, although the case is reported

under the title of "Tetany of the Newborn" it is not a proved one. The author herself states "The most we can say is that we cannot prove its absence, especially since the spinal fluid calcium was somewhat low though I do not believe that the baby had tetany." Guild also quotes the history of a ten-day-old infant (Case 3 on p. 50 of her report) who had had severe diarrhea for three days followed by twitchings of the face and arms for several days with a blood calcium content of 6 mg per cent and a phosphorus of 9.5 mg per cent. However examination of the spinal fluid revealed a definite xanthochromic discoloration and the symptoms did not yield to calcium therapy. An overdose of parathormone resulted in a rise of the blood calcium and phosphorus levels at the time of death to 20 mg and 15 mg respectively. At necropsy normal parathyroids and a large intracranial hemorrhage were found. The absence of other hemorrhages particularly of intestinal hemorrhages was interpreted as pointing against the overdose of parathormone having been the cause of death. Apparently the case was one of tetany combined with an intracranial hemorrhage. The persistence of symptoms in spite of calcium therapy was probably due to the intracranial hemorrhage.

Shortly thereafter Bloxson and Nicholas⁹ described two cases of twitching occurring during the first day of life. Since the calcium content was not determined in their first case, the case remains unproved. Although the blood calcium content was relatively normal (9.2 mg) in their second case, the ionizable calcium concentration was low.

In February, 1934 Craig¹⁰ reported an authentic case of low calcium tetany in a newborn infant. Generalized convulsions and facial twitchings occurred from the ninth to the fifteenth day. A diagnosis of cerebral hemorrhage was made. On the sixteenth day the calcium and phosphorus concentrations were 7.3 mg and 4.4 mg respectively. Oral calcium therapy was given but the convulsions continued (52 and 33 seizures on the seventeenth and eighteenth days respectively). Following an intramuscular injection of calcium on the eighteenth day, the symptoms promptly ceased. Although the Chvostek phenomenon had been positive, carpopedal spasm and laryngospasm were not present at any time during the illness.

Gaberman¹¹ is quoted by Bass to have found a blood calcium concentration of 5.3 mg in a newborn infant with vomiting, hyperpyrexia, and convulsions. This case has not been reported to date.

The increasing frequency of occurrence of these cases of low calcium tetany of the newborn surely cannot be due to an increasing incidence of the syndrome. It is more likely that the pediatrician has been made aware of the existence of the disease in the newborn by the report of the early cases mentioned previously. He is now alert for any clinical manifestations of tetany and realizes the necessity for determining the cal

cium content of the blood in any case of twitches or convulsions of unexplained etiology in the newborn. It is likely that a fair proportion of the cases of convulsions in newborn infants which terminated fatally in the past and were diagnosed as so called "cerebral injuries" actually may have been unsuspected cases of low calcium tetany in the newborn.

A second proved case of low calcium tetany has been observed by the author within a period of fifteen months.

Baby K, a male infant, weighing 6 pounds 12 ounces, was delivered by means of low forceps by Dr. Hellman at the Lenox Hill Hospital. At the time of delivery, the infant's oral and nasal passages were filled with meconium which was removed digitally. The infant was somewhat cyanotic, crying feebly from time to time. The temperature was subnormal (97.2°F). Toward the end of his first day of life, the temperature rose to 103.8°F , and the respiratory rate rose to 75 per minute. Physical examination revealed the presence of labored respiration, dilatation of the alae nasi, cyanosis of the lips and of the nail beds of the fingers and the toes, and dullness with crepitant râles at the left base. A positive Chvostek phenomenon was elicited. A diagnosis was made of a pneumonia secondary to the aspiration of meconium at birth. CO_2 and oxygen were administered in an oxygen tent, the color improved, and the respirations became less labored. After ranging between 102° and 103°F for thirty six hours, the temperature fell to normal on the third day. During the febrile stage, fluid was supplied by clyses, and an intramuscular injection of paternal whole blood (50 cc) was given toward the end of the second day. Several hours later, slight transient twitches of the facial and extremity muscles were observed but did not again recur during the course of the pneumonia. The Moro test was negative for any evidence of cerebral injury. The chest signs gradually cleared. The respiratory rate remained elevated although the respirations seemed less labored, and the temperature remained normal.

A formula consisting of evaporated milk, water, and dextrimaltose was well taken and the infant, after having gained initially as a result of the retention of the fluid given by clysis, continued to gain in weight. On the fifth day a second intramuscular injection of paternal whole blood (30 cc) was given and was well absorbed. The infant seemed completely well.

Suddenly at the end of his seventh day of life, twitchings of the legs, arms, and eyelids were noted, lasting for several minutes and being accompanied by a slight degree of cyanosis. Following this, the infant slept well and took his feedings eagerly. On physical examination the fontanel was not bulging, the reflexes were normal, but the Chvostek sign was still positive. The reaction to the Moro test was again normal in character.

Eight hours later, on the eighth day of life, twitchings of the arms and legs were again noted lasting for about half a minute, being followed by a generalized convulsion lasting for three minutes. Physical examination revealed a normal Moro phenomenon but, although a much more positive Chvostek reaction was elicited, no carpopedal spasm or laryngospasm was present, the chest was clear, but a thin purulent discharge was observed in the right ear canal. A tentative diagnosis of low calcium tetany of the newborn secondary to the pneumonia and the subsequent acute right otitis media was made. A specimen of blood was taken for chemical analysis and 10 c.c. of calcium gluconate (10 per cent solution) were given intravenously through the same needle. The calcium content of the blood was found to be 7.6 mg per 100 cc of serum. (The phosphorus content was not determined because of an insufficiency of serum in the specimen sent for the determination.)

Thereupon one ampule of calcium gluconate (10 c.c. of a 10 per cent solution) was given intravenously each day. Calcium gluconate and viosterol in increasing doses were given orally. Two injections of the calcium gluconate were given intramuscularly during the first two days of therapy.

No more twitchings or convulsions were observed until the eleventh day of life (on the third day of calcium therapy), when twitching of the facial muscles for a duration of two minutes was noted. The intravenous and the oral therapy were continued throughout the second and third weeks, for a second blood determination done on the fifteenth day of life (on the eighth day of therapy) revealed a blood calcium and phosphorus content of 7.5 mg each per hundred cubic centimeters of serum. The general condition continued to improve, and the infant gained in weight although the thin purulent aural discharge persisted without a febrile reaction. The Chvostek phenomenon remained positive until the end of the second week of life. Carpopedal spasm and laryngospasm were not observed at any time during the illness.

The intravenous therapy was discontinued after fourteen daily injections had been given, but the oral administration of calcium gluconate (45 grains per day) and of viosterol (30 drops per day) was continued. A third blood calcium determination seventeen days after the institution of calcium therapy revealed a blood calcium content of 9.3 mg per 100 c.c. of serum. The infant was discharged three days later at the age of three weeks after a gain of 2 pounds and 5 ounces over its birth weight. Save for the discharge from the right ear which had lessened, physical examination showed him completely normal. The mother was instructed to continue the daily oral administration of calcium gluconate and viosterol for several weeks to ensure the nonrecurrence of symptoms of tetany.

COMMENT

The only signs or symptoms of tetany present in this patient were the positive Chvostek phenomenon present from birth and the twitchings and convulsions occurring on the seventh and eighth days. Laryngospasm, carpopedal spasm and subcutaneous edema were not present at any time during the course of illness.

This case serves to emphasize the fact that laryngospasm and carpopedal spasm, which are ordinarily considered cardinal signs of tetany, need not necessarily form part of the symptom-complex. The presence of the positive Chvostek phenomenon had not been regarded as significant prior to the development of the twitches and convulsions for this sign is observed frequently in healthy newborn infants who have normal blood calcium concentrations and do not manifest clinical symptoms of tetany (Stevenson, Mitchell and Koch¹²). The transient twitching of the face first noted on the second day of life during the course of the pneumonia, must have been the first symptom of active tetany although its significance was not recognized at the time. The twitchings of the muscles of the face and extremities followed by convulsions noted on the seventh day were recognized as manifestations of active tetany, and treatment was instituted promptly.

It is of interest to note that the presumptive diagnosis of tetany of the newborn had been made and intravenous treatment begun prior to the analysis of the specimen of blood for its calcium content. The di

agnosis was based on two factors first, the absence of any signs pointing toward cerebral injury or meningeal involvement such as an abnormal response to the Moro test, bulging of the anterior fontanel, or the changes in the reflexes noted in meningeal irritation, second, the presence of unexplained twitchings and convulsions occurring during the course of infection in a newborn (the aspiration pneumonia and the purulent otitis media)

Infection may precipitate the development of symptoms of tetany in an older infant, and that this occurs in cases of latent infantile tetany (low calcium concentrations without active symptoms) is well recognized. Similarly, in the newborn latent tetany can exist as is shown by Stevenson, Mitchell, and Koch's¹² case of a normal newborn infant with 7.3 mg of calcium but without clinical symptoms. It would seem possible likewise in the newborn for an infection in such an infant to cause a precipitation from the latent stage (without clinical symptoms) into an active or manifest tetany, so that presumably, in the case quoted herein, the blood calcium may have been low at birth, and a latent form of tetany may thus have been present only to have symptoms occur as a result of the infection.

Certainly in the case of low calcium tetany reported herein, the diagnosis might have been completely overlooked in the absence of other symptoms (laryngospasm or carpopedal spasm) if the rôle of infection in precipitating symptoms of active tetany had not been so visualized. Had one waited for the development of such suggestive signs as laryngospasm or carpopedal spasm before venturing the diagnosis of tetany and applying the proper therapy, the outcome might have been fatal. This case emphasizes the necessity for blood calcium determinations in all cases of convulsions or twitches in the newborn of unexplained etiology, even in the absence of other confirmatory evidence of tetany (laryngospasm, carpopedal spasm).

Another point of interest is that the blood calcium content remained relatively unchanged after the first week of intensive calcium therapy even though the infant was symptom-free after the third day of therapy. It was not until the end of the second week of therapy (after fourteen daily intravenous injections of 10 cc of the 10 per cent solution of calcium gluconate) that the calcium concentration in the blood reached the level of 9.3 mg. Even then, to prevent recurrence of symptoms from a subsequent lowering of the calcium content of the blood such as occurred in Powers'¹³ case, oral calcium and viosterol medication was continued for three weeks after the baby's discharge from the hospital.

SUMMARY

1. A case of low calcium tetany in a newborn infant is reported. Facial twitchings first occurred on the second day of life during the course of aspiration pneumonia. Twitchings recurred on the seventh

day of life and again on the eighth day, followed by convulsion. The blood calcium content was 7.6 mg. Intensive therapy was instituted. Although symptoms of active tetany ceased after the third day of therapy, the blood calcium content was relatively unchanged (7.5 mg.) at the end of a week of therapy and was raised to 9.3 mg. only after two weeks of intensive intravenous and oral calcium therapy. Vitamin D in the form of viosterol was given to increase the absorption of calcium through the intestinal tract.

2 This is the second proved case of low calcium tetany in the newborn during the first three weeks of life observed by the author within a period of fifteen months.

3 The presence or absence of the Chvostek phenomenon is not of diagnostic significance. Although laryngospasm and carpopedal spasm may be present they must not necessarily form part of the symptom complex. The occurrence of convulsions or twitchings of unexplained etiology in a newborn infant even in the absence of other signs and symptoms of tetany, necessitates a blood calcium determination to establish or rule out low calcium tetany.

5 The increasing frequency of reports of low calcium tetany in the newborn is obviously not due to an increased incidence of the syndrome but rather to increased watchfulness on the part of the physician and routine blood calcium determinations in cases of convulsions or twitches of unexplained etiology in the newborn.

6 If the calcium content of the blood were determined routinely in all such infants, it is probable that low calcium tetany would be found much more commonly in the newborn period than has hitherto been the case.

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HEMIHYPERTROPHY

REPORT OF FOUR CASES

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LOS ANGELES, CALIF

THE literature on hemihypertrophy is accumulating, but very few studies have been made outside of the work of Gesell¹ who reports the material up to 1921. He considers the condition the result of some developmental disturbance dating back to an early embryonic stage and also as "a form of asymmetrical twinning due to a possible deviation in the normal process of twinning."

The majority of cases occur in males, the right side is usually involved, nevi may or may not be present. The mentality in some patients is abnormal, in others it seems to be normal. Three of our patients are apparently normal, one is definitely abnormal.

The sebaceous glands in some instances on the affected side seem to have an abnormal secretion, the sweat glands are abnormally active, the growth of hair is thicker, the nails grow more rapidly, and also there is an earlier eruption of teeth. The temperature on the affected side is reported to be one or two degrees higher than on the other.

Some patients have an extreme enlargement of the fingers or toes on the affected side as the only abnormal hypertrophy.

Pathology—There is a unilateral hypertrophy of the soft structures, the bones, and occasionally of the internal organs, with the pituitary and sella turcica usually normal. In the literature some of the patients are stated to look older on the affected side than on the other. The half of the brain opposite to the affected side has been reported as enlarged or hypertrophied. *Microscopic examination* shows that there is an increase in the interstitial connective tissue and in the tissue of the peripheral nerves.

Differential diagnosis from hemiatrophy is not difficult as there is no atrophy present.

The prognosis is good.

The method of treatment is usually determined according to the parts affected. For some, orthopedic appliances are helpful, and in some cases, such as certain face abnormalities, operative interference is indicated.

From the California Babies Hospital and the Pediatric Department of the California Hospital.

In our search of the literature no case of congenital hemihypertrophy is recorded, some authors going so far as to state the condition is not hereditary. Our cases of mother and daughter are therefore unusual.

CASE 1—D. B. was first seen Mar 3, 1932, at the age of nine years and one month. He was the first child, delivered by forceps at the seventh month of gestation. His birth weight, 6 pounds 8 ounces does not correspond to the gestation period. He was breast fed for two months, then artificially fed. He was given cod liver oil and orange juice and some heliotherapy. The first tooth erupted at the sixth month, and he was walking and talking (?) at the end of the first year. He has had measles, pertussis, frequent colds, and a tonsillectomy in 1930. Parental history is unim-

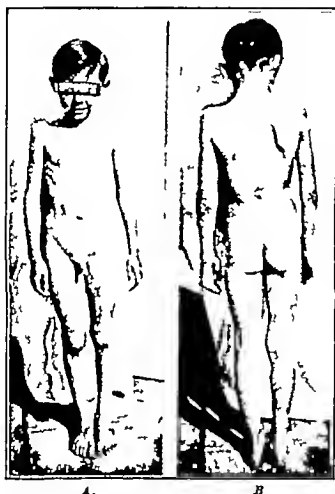


Fig 1—Case 1. D. B. A. Note difference in size of legs. B. Note scoliosis.

portant for the condition under consideration. When seen he complained of frequent colds and a tendency to wheezing. The physical asymmetry was noted on examination, and the mother stated that when the lad was four years old he had an injury over the left mastoid, at which time the difference in the legs was noted.

Physical examination shows the right hip, leg, and foot slightly larger than the left. A compensatory scoliosis to the left is marked.

The measurements of the shoulder	Right arm	Left arm
to tip ulnar process	43.7 cm.	43.2 cm.
Palm of hand circumference	15.5 cm.	14.5 cm.
Ant Sup spine ilium to inner malleolus	Right leg	Left leg
	69.0 cm.	68.5 cm.

Right thigh is 1 cm. larger than the left.

The right calf of the leg is 1 cm larger than the left

He wears a size larger shoe on the right foot than on the left

He was referred to Dr H W Spiers for orthopedic consultation and his report shows "a marked difference in size and length of the left side, from the pelvis downward, as compared with the right There is a slight beginning structural scoliosis X ray films were made of the pelvis, spine, knees, hands, and feet They show changes in size and shape of the left pelvis, left thigh, and left foot It is noted throughout that there is some delay in ossification of the smaller bones, particularly in the hands "

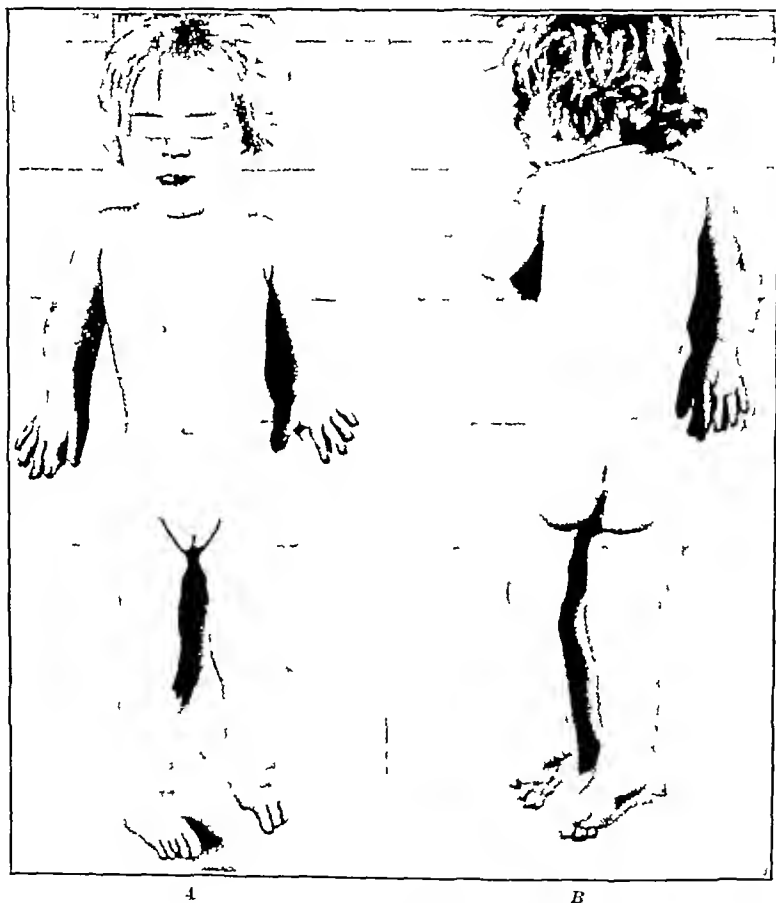


Fig 2—Case 2 J B May 1934 Hemihypertrophy and congenital heart disease. (The distance between the lines is 5 inches)

Corrective shoeing and exercises were prescribed

Mentally this boy is normal for his age

CASE 2—J B, aged nine months, came to the Anita Baldwin Clinic Dec 28, 1931 She was the second child, delivered normally, but not breast fed. Birth weight was 6 pounds 4 ounces The older child, a girl, is normal physically and mentally The family history is irrelevant except for the mother whose history is detailed in the next report

On physical examination, a small nevus 1 cm in diameter was found on the right shoulder. The musculature was fair, but the infant could not sit alone. The anterior fontanel was small, the sagittal suture, open from the glabella to the posterior fontanel. The left side of the skull looked smaller than the right, the left arm and leg shorter than the right side. The left middle and ring fingers were flexed and could not be extended.

The back of the head was flattened, and the fingers and toes clubbed. The lips were cyanotic. When the child cried, the skin was darkened.

The mother stated that the infant did not use her left arm until she was four months old. At birth the left leg was extended upward on the abdomen. At the present time she did not extend the left leg fully. Talipes valgus of the left foot was present. The left hand could not be completely supinated and the left ear protruded more than the right.



FIG. 3.—Case 2. Mrs. B. A. The tilted head shows the slight difference between the sides of the face. The hands show the difference to a slight extent. B and C. Posteriorly the scoliosis is marked, as is the leg length. The difference in circumference was not noted except by measurements.

The lungs and abdomen presented no abnormalities, but the heart had a harsh basal systolic murmur most pronounced to the left of the sternum the murmur being transmitted in all directions—probably pulmonary stenosis. The reflexes were not especially active, though present.

Under treatment she improved so that when seen Mar. 21, 1933 at the age of one year she could sit alone and had five teeth. The roentgenograms at this period showed normal epiphyseal growth for her age equal on both sides for arms and legs. The blood Wassermann reaction was negative.

Dr. H. W. Spiers examined the infant July 27, 1933, and reported: 'The infant is right handed. The left arm is approximately $\frac{1}{4}$ inch shorter than the right, the left leg is $\frac{3}{8}$ inch shorter than the right. The circumference of the left calf of the leg is $\frac{1}{8}$ inch less than the right, while that of the left thigh is $\frac{1}{4}$ inch less than

the right. The left leg is bowed below the knee, and the foot is in talipes valgus. Asymmetry of the face is evident. The roentgenograms confirm the clinical findings though no congenital variation was found except in size."

CASE 3—Mrs. B, the mother of J. B., was born in June, 1905, hence at the time of her visit was twenty six and one-half years old. Her birth weight was 6½ pounds, delivery was normal, and she was breast fed. When she was nine years old, a slight limp was noticed, this was very marked when she was sixteen years old. She menstruated first at the age of fifteen years. There was no record of a similar condition on either side of her family. She was the second child of four, the others being normal. She cut her first tooth at six months and walked at 15 months. The blood Wassermann reaction was negative.

Dr. H. W. Spiers reported the results of the examination:

"The left leg is 1½ inches longer than the right, the left calf of the leg ½ inch larger than the right, the left thigh is the same as the right. The arm circumference



Fig. 4—Case 4. M. G. A. Facial expression showing mental weakness. B and C. Anterior and posterior views showing difference in legs.

is about the same. There is slight facial asymmetry, the left side being wider and fuller than the right. The spine shows a marked degree of structural scoliosis."

CASE 4—M. G., female, aged five months, entered the clinic June 23, 1928. The father was sixty years old, mother, thirty eight years old. There were three other children living and well. The child was born at full term, weighing nine pounds, and was breast fed. Her disposition was reported as good, and she slept well. Bowel movements were regular.

On physical examination the right side of the body, face, and extremities were all noted to be larger than the left.

In January, 1929, when she was eleven months old, roentgenograms were made (Dr. Snure).

The film of the lower half of the body showed no difference in osseous structures, the femur at lower end on right side appeared larger because it was raised slightly from the film. Soft tissues appeared to be about 50 per cent increased in size. The

film of the upper half of the body showed an enlarged distorted heart shadow probably a combination of several heart lesions. Density in the upper mediastinum was increased—probably heart and large vessels instead of thymus. The trachea was displaced toward the right. Right humerus appeared slightly larger than the left.

Only three ossification centers were present in the left wrist as against five in the right wrist when carpal bones alone are considered, the left wrist would suggest an age of slightly less than two years. The right suggests an age period of about four years.

A roentgenogram of the whole body by Dr K. S. Davis of St Vincent's Hospital, in April, 1929, showed a marked difference in the two sides of the body especially in the extremities, the left arm being 50 per cent smaller than the right and the left leg showing about the same difference in size. There was noted the presence of five carpal bones in the right wrist and only three in the left wrist. There were six well-developed tarsal bones in the right ankle and the same number in the left ankle, but not as well developed as in the right. The left tibia and fibula were shorter and narrower than the right. The left femur was the size of the right. The left radius and ulna were considerably smaller than the right. The left humerus was smaller and shorter than the right and its epiphysis not as well developed or as distinct as the right. The skull showed but little difference in the two sides on the basis of the roentgenographic findings.

Another roentgenogram in January, 1931, by Dr Snare showed that the heart outline varied from normal in that the outline was extended about 1 cm. more than average from the aortic arch on the left side halfway down to the left apex. Whether this was an enlargement of the left auricle or pulmonary artery could not be determined.

The size of the left arm appeared to be 50 per cent that of the right. The same number of epiphyses were present in each wrist, but those in the right were 50 per cent larger than the left. The ossification center for the proximal epiphyses of the radius was distinct on the right side and absent or questionable on the left. Knee joints, except for size, showed no variation, the right being 50 per cent larger than the left. The left leg was $2\frac{1}{2}$ cm shorter than the right. Single anteroposterior film of the pelvis showed the right side longer and larger than the left.

No orthopedic treatment was recommended by the orthopedist as the mental condition of the child prevented cooperation. The blood Wassermann reaction was negative.

During the time she was under observation in the clinic, she was given cod liver oil and had an attack of pertussis from which she made a complete recovery. In March, 1929, she was given thyroid gland substance 1 grain daily which was continued to November of the same year but with no apparent effect on the mental or physical condition.

The child was subject to violent attacks of screaming, she would throw herself about, and it was with difficulty that the attendants could keep her from doing injury to herself. She was a low type of imbecile mentally unresponsive to any person.

SUMMARY

Four cases of hemihypertrophy are presented two being in mother and daughter. One subject is male, the others female. Three apparently are mentally normal, one, abnormal, one patient has a nevus the others none. The right side is involved in the male and two females, and the left in one female.

No abnormalities, such as any excessive sweating, sebaceous secretions, hairy growth, or nail hypertrophy that are mentioned by some authors, were noted. One female infant had in addition a congenital cardiac lesion.

The treatment is essentially orthopedic to balance the body structure.

CONCLUSIONS

Hemihypertrophy is not as uncommon as has been suspected. The careful physical examination of all infants and children should reveal the condition if it is present. The statement that the condition is not hereditary cannot be proved, as we report a mother and daughter with the same complaint. There is nothing abnormal in the epiphyseal centers of these patients, so far as the roentgenograms show. The exact etiology has not been determined, but it is something in the early embryonic stage of development.

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STRAMONIUM POISONING

A REVIEW OF THE LITERATURE AND REPORT OF TWO CASES

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REPORTS of cases of poisoning in children from the ingestion of stramonium seeds are relatively uncommon, despite the prevalence of the Jimson weed.

Jimson weed, or as it is often called, Jamestown weed or thorn apple is known to botanists as *Datura stramonium* a species of the Solanaceae or nightshade family to which also belong the red pepper, tobacco tomato, belladonna and bittersweet plants. It is a rank scented tall much branched narcotic annual herb attaining a height of from three to six feet with five lobed trumpet shaped flowers, and broad ovate shallowly lobed leaves. The fruit is a four-celled spinous capsule containing many small black brown reniform seeds which measure approximately three by two millimeters. The plant flowers in late spring and the fruit ripens in early fall.

The leaves and seeds of the *Datura* contain hyoscyamine atropine, and scopolamine in varying amounts. In some analyses as much as 0.33 per cent of the alkaloid atropine, has been found in the seeds and about 0.2 per cent in the leaves.

A perusal of the early literature indicates that the hypnotic and narcotic effects of members of the *Datura* species were known to the ancients. The capacity of the plant for causing forgetfulness and for rendering victims susceptible to suggestions is recounted in the *Iliad* which describes the activities of Ulysses' men after they had drunk of Circe's drugged wine.

Shakespeare^{1a, b} in *Romeo and Juliet* alludes to the mandragora as the potion which the holy friar gave to Juliet to make her appear dead. In *Antony and Cleopatra* this was the powder that Cleopatra begged of Charmian that she might sleep out the gap of time when Antony was away.

The origin of the name Jamestown weed, which is applied to the variety of *Datura* native to this country, dates back to the year 1676 when a group of men under Captain John Smith was sent to Jamestown Va. to quell the Bacon rebellion. For comparison with the cases here reported it is interesting to note the effect of the ingestion of the leaves of the plant on these men as recorded by Beverly^{1a, b}

From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals, Boston.

This being an early Plant, was gather'd very young for a boil'd salad, by some of the Soldiers sent thither, to pacifie the troubles of Bacon, and some of them ate plentifully of it, the Effect of which was a very pleasant Comedy, for they turn'd natural Fools upon it for several Days One would blow a Feather in the Air, another would dart Straws at it with much Fury, and another stark naked was sitting up in a Corner, like a Monkey grinning and making Mows at them, a Fourth would fondly kiss and paw his Companions, and sneer in their Faces, with a Countenance more antik than any in a Dutch Droll. In this frantik Condition they were confined, lest they in their Folly should destroy themselves, though it was observed that all their Actions were full of Innocence and Good Nature Indeed, they were not very cleanly, for they would have wallow'd in

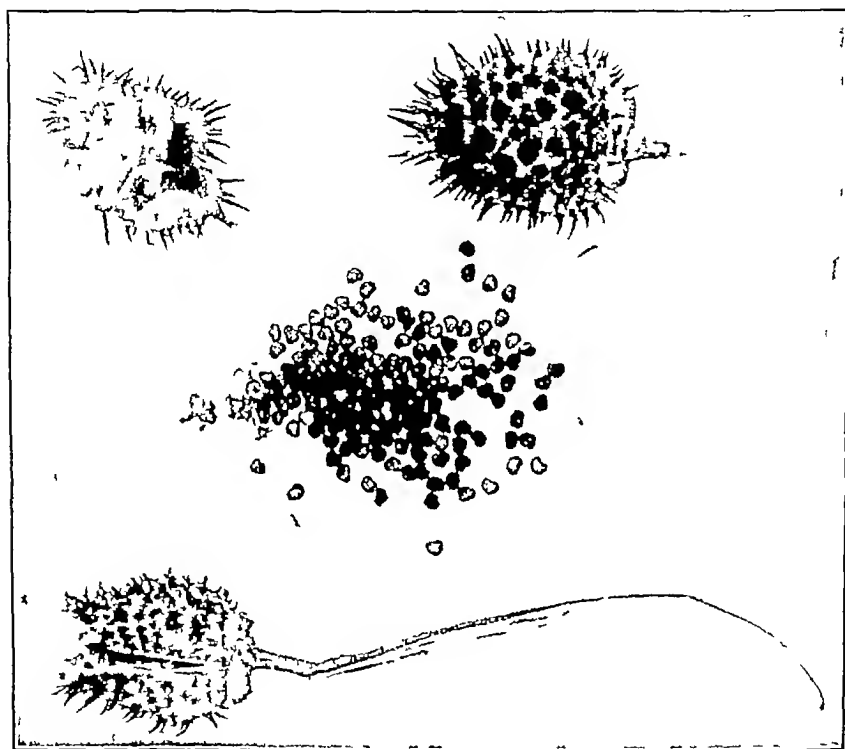


Fig 1—Full size reproduction of fruit showing spiny pod with reniform seeds

their own Excrements, if they had not been prevented. A Thousand such simple Tricks they play'd, and after Eleven Days, return'd themselves again, not remembering anything that had pass'd.

Undoubtedly, it was this same drug that was used by the Algonquins and other tribes of Indians in their huskanawing ceremony for the initiation of their boys into the dignity of manhood as described by Beverly^{1b}

The Pueblo Indians of Mexico used the ground seeds of the Nacazcul (a South American variety of the *Datura stramonium*) mixed with pitch, because of the analgesic properties of the preparation, for setting

bones and dislocations. Warning was given, interestingly enough against the use of excessive amounts of the powder, lest the patient be seized with madness and become the victim of 'various and vain imaginations.'

In the more recent literature cases of stramonium poisoning have been reported from various parts of the world. Garvin and Ruh⁸ describe an outbreak of poisoning among thirty boys in an orphanage with resultant pandemonium. The Jimson weed was later found in the play yard. Watt¹⁸ and Breyer Brandwyk report an outbreak of stramonium poisoning among forty-eight mine boys in Southwest Africa. These patients had eaten cooked beans containing the seeds of the stramonium plant which grows wild in that area the contaminating seeds having been harvested unnoticed with the bean crop. Ismael⁹ also describes cases of poisoning from gruel in which the seeds had been harvested with wheat. Additional cases of poisoning in children have been reported by Wilcox²⁰ and Grinnon⁸ in the United States by Howle⁸ and Parkinson¹⁸ in Australia, by Estapé and Bloise⁸ in Uruguay by Neyron¹⁸ in France, by van Ravenswaay¹⁸ in Netherlands, and by Mukopodhya¹² in India.

At the Kasr-el Ainy government hospital at Cairo according to Ismael,⁹ datura poisoning ranks second in frequency to acute alcoholic intoxication among those brought into the hospital in an unconscious state. In Egypt and India datura seeds or their powder are added to food or beverages to facilitate robbery, or for homicidal purposes. Lenoir¹⁰ describes the use of this drug among the inmates of the convict prison at New Caledonia. He reports that those given the drug usually become possessed of an idea to protect their hoard and that they usually run to the hiding place unearth it and thus facilitate robbery.

Another case of poisoning has been reported by Sboemaker,¹¹ from Philadelphia. He described the case of a twenty-six year-old negro laborer who drank an infusion of the leaves from the Jimson weed as spring tonic.

The Jimson weed is very common throughout the United States and tropical regions of the Old World. During the summer and fall small children playing in the garden or in the woods are attracted by this large weed and its fruit and, mistaking it for some edible fruit, eat it in relatively large amounts. Because of the potential danger from this source, a report of two cases of stramonium poisoning together with a review of the subject is thought to be of value.

CASE 1.—H. C., a five-year-old white boy, was admitted to the Children's Hospital on Oct. 24, 1932, because of dilated pupils, thirst, increasing disorientation and motor excitement of five hours' duration.

The child had developed normally and had enjoyed good health until the onset of his present illness.

The patient had been playing in the yard with other children during the morning, but his mother noticed that he entered the house several times for drinks of water which he took with avidity. Shortly after the onset of the thirst and six hours before entry, it was noticed that the pupils of his eyes were widely dilated and that his lips were dry and purple. He was given 3 teaspoonfuls of castor oil and was put to bed, where he slept for two hours.

Three hours before admission he awakened from his sleep, was incoherent in his speech, cried out lustily, was unsteady on his feet, and reached for imaginary objects. Jerking movements of the arms and legs were noted. These symptoms increased in intensity, and his family physician recommended hospitalization.

The patient was a well developed boy of five years with slightly flushed face, tossing wildly about in bed, picking at imaginary objects in the air, and speaking incoherently. The skin was warm and dry, and the throat was dry and red. The pupils were dilated and fixed, the heart rate was 124 per minute.

Atropine poisoning was suspected because of the widely dilated pupils, dry throat, tachycardia, and motor excitement. Soon after entry the patient vomited some orange juice in which was mixed green pulpy material, containing three small reniform seeds each about three millimeters in diameter. The stomach was then lavaged with a 4 per cent solution of soda bicarbonate, but no more seeds were found. The stage of excitement continued for several hours, but gradually he became quiet and spent a restful night. Twelve hours later the child was well oriented and calm, but the pupils continued to be dilated for another twenty-four hours.

The seeds expelled in the vomitus were identified by Dr. Reid Hunt, professor of pharmacology at Harvard Medical School, as stramonium seeds which contain both atropine and scopolamine. It was suggested that the rash, vasodilatation and fever, characteristic of atropine poisoning, were absent because of the inhibiting effect of scopolamine.

Further communication with the parents of the patient revealed the presence of the Jimson weed in their yard. The patient recognized a pod and acknowledged eating the seeds for "peanuts," stating that he cracked open the pods with "a pliers."

The patient made an uneventful recovery, with an afebrile course and was discharged home six days after admission with a diagnosis of stramonium poisoning.

CASE 2—E. P., a four and one half year old white girl, was admitted to the Children's Hospital on Sept. 7, 1933, because of dizziness, delirium, flushed face, and dilated pupils of seven hours' duration.

The child had been outdoors playing with her sisters and some neighbors during the afternoon, and when she was called to supper, it was noted that she was acting queerly. Her playmates said that she was dreaming. She talked incoherently and gave irrelevant answers to questions. When offered water, she spat it back and continued to spit "as if her mouth were full of cotton." Her mother noted that she was flushed and that her eyes were "starey." She was given an enema. Her family physician suspected drug poisoning, and finding no possible causative drug in the house, advised admission to the hospital for observation.

On arrival at the hospital, the child was irrational, making purposeless gyrations with her arms, going through the motions of blowing kisses with her hands, and of plucking things out of the air. Except for flushing of the face with circumoral pallor, dilated fixed pupils, a dry mouth covered with sticky saliva, and a rapid bounding pulse, examination was negative.

The mother was carefully questioned concerning the ingestion of atropine or of the possibility of the child's having eaten any weeds or plants, but any such knowledge was denied.

The admission diagnosis was atropine poisoning but to rule out a possible early encephalitis, a lumbar puncture was performed which yielded a normal spinal fluid. Gastric lavage yielded nothing of aid in the diagnosis. She was given $\frac{1}{80}$ grain of pilocarpine and $1\frac{1}{2}$ grains of sodium luminal, subcutaneously.

Upon returning home, the mother awakened the other children and on close questioning found that the patient had eaten seeds from a pod which one of the neighbor children had brought into the house. The mother found one of the pods and brought it to the hospital. The pod was recognized by Dr Hunt as the fruit of the Jimson weed.

In the course of twelve hours the patient became rational and the pulse rate dropped to normal. The pupils continued to be dilated for twenty hours. At no time was the temperature elevated.

The child made an uneventful recovery and was discharged two days after entry with a diagnosis of stramonium poisoning.

The symptoms of stramonium poisoning are variable in their degree and nature because of variations in the amount of the respective alkaloids atropine and scopolamine. Depending on the amount of the drug and the form in which it is taken, the onset occurs from ten minutes to four hours after ingestion. In criminal poisoning, in which the powdered drug is taken in food or beverage the onset of symptoms is very rapid, but in children in whom the leaves or seeds are taken without being thoroughly chewed the symptoms are more gradual in their onset.

According to Ismael* there are two forms of symptoms the maniacal form from seed poisoning and the comatose form usually seen when the leaves are the causative agent. Variations between these two forms are not uncommon.

In the maniacal form the patient is boisterous his speech is impetuous and incoherent his actions are impulsive and exaggerated he reaches for imaginary objects and attempts to pull threads from his finger tips. His activity may be of a destructive nature manifested in attempts to harm himself or those about him. After a variable period of time, usually from twelve to twenty four hours the maniacal stage may pass into the comatose form which is marked by degrees of unconsciousness varying from mild stupor, from which the patient may be easily aroused, to profound coma in which the temperature is subnormal, the pulse feeble and the respirations slow and stertorous, accompanied by a deep cyanosis.

One of the earliest symptoms of poisoning is extreme thirst, and the patient attempts to drink large quantities of water. This may initiate vomiting which however is not a constant finding due to relaxation of the pyloric sphincter. On the other hand, constipation and urinary retention are quite constant, due to the inhibitory action of the drug on the parasympathetic system. Convulsions of a tetanic nature are de

scribed by van Ravenswaay¹⁸ in one of his cases, and Ismael⁸ describes clonic convulsions with retraction of the neck and opisthotonus simulating meningitis

Objectively, the pupils are dilated and fixed, the skin is dry and flushed with a diffuse nonpunctate erythematous rash, and the pulse is rapid and weak with a tendency to diastolic murmurs. The temperature is variable, but in several cases, notably those reported by Garvin and Ruh,³ and van Ravenswaay,¹⁸ a fever as high as 105° F is recorded. Because of salivary inhibition and vasodilatation, the pharynx and tonsillar fauces may appear intensely red and injected

Ordinarily, the symptoms subside in twelve to forty-eight hours, and the patient becomes quite normal except for ocular dilatation, which may continue for seven to fourteen days. Characteristically, the patient remembers nothing of his condition during the previous period. Although recovery is usually complete, Lenoir¹⁰ described three cases in which insanity persisted, and a case of permanent amentia is described by Zakarias²¹. When large amounts of atropine are present in the seeds, the symptoms are prolonged and serious. It is the amount of scopolamine that is present which masks the symptoms usually associated with atropine poisoning and which accounts for the lack of fever, rash or evidences of vasodilatation. The effects from this drug are not so serious or lasting

The treatment of stiamonium poisoning is directed toward preventing further absorption of the drug and toward symptomatic relief. The first step is the removal of the poison from the gastrointestinal tract. This may be accomplished by stomach lavage with water. The use of 4 per cent tannic acid solution is recommended by Gimlette,⁴ as this precipitates the alkaloids. This author suggests the later use of potassium permanganate solution in 1:5,000 dilution to oxidize any of the remaining drug. In children, in whom gastric lavage is difficult, induction of emesis by apomorphine subcutaneously, or by ipecac orally, is justified. The removal of the drug from the intestines may be hastened by large doses of magnesium sulphate by mouth, in urgent cases, the use of croton oil by mouth or surgical pituitary extract subcutaneously has been recommended.

After the amount of ingested drug has been reduced to a minimum, efforts should be made to induce rest and quiet. The patient should be kept in a quiet, dark room with careful nursing supervision, under restraint, if necessary, to prevent injury. Sedatives such as paraldehyde or the barbiturates may be given. Warm packs are useful in obtaining relaxation, and the diaphoresis so obtained is said to hasten excretion of the drug. In severe cases, a 25 per cent solution of magnesium sulphate given intramuscularly may be helpful, care being taken to avoid excessive fall in blood pressure.

The use of morphine has been suggested to secure rest, but it probably should be given sparingly because of the synergistic action of morphine with atropine and scopolamine.

Pilocarpine, the physiologic antidote, having an antagonistic action on the parasympathetic system, has been used in the treatment of stramonium poisoning, but because of the difficulty in estimating the amount of the offending drug that has been ingested, accurate use is impossible. When used, pilocarpine should be administered in repeated small doses until the desired effect has been obtained. Pilocarpine is contraindicated in elderly people because of its tendency to cause pulmonary edema instead of diaphoresis.

Fortunately the number of fatalities from accidental poisoning with stramonium is small. Variable amounts of the drug have been found in fatal cases, but the lethal dose is difficult to estimate since the toxic symptoms would necessarily be caused by the digested seeds, rather than by those found in the alimentary canal. McNally¹¹ in 1915 reported the case of a seven year-old boy who died fourteen hours after the ingestion of the seeds. During this time he had shown the clinical evidences of excitement followed by coma and dry stertorous respirations. At autopsy several hundred small petechiae over the epicardium were found. The lungs were distended with hypostatic congestion in both bases, and a few subpleural hemorrhages were noted. One hundred seeds were found in the gastrointestinal tract.

McNally¹¹ also recorded the death of a child of two and one-half years after the ingestion of sixteen seeds. An Indian laborer died in seven and one-half hours. Examination of the stomach contents from the case revealed eighty nine seeds.

In addition Hursbberger⁷ in 1909 mentioned the death of a three year-old child, resulting from the ingestion of stramonium seeds. Pam mol¹⁴ refers to two cases about metropolitan New York in boys under five years of age. One of these patients was known to have obtained the seeds from a plant in a public park.

According to Lenoir¹⁰ Gimlette,⁶ and Ismael⁸ deaths from criminal poisoning are more common since the powdered drug is used. The dosage is difficult to estimate and, whereas the amount given is intended only to incapacitate the victim to facilitate robbery death often results from overdosage. Lenoir described the fatal case of a convict who used the drug as a means of suicide. Falck as quoted by Kober⁹ in 1906 stated that death occurred in 11.6 per cent of the collected cases of atropine and hyoscyamine poisoning.

SUMMARY

Historical references to the use of stramonium are noted, and the recent literature has been reviewed with respect to the biology and

pharmacology of the drug together with the incidence, symptomatology, and treatment to be followed in cases of poisoning resulting from its ingestion

Two cases of stramonium poisoning in children, with complete recovery, are reported.

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143 PARK STREET

DENTAL CARIES

A CALCIUM AND INORGANIC PHOSPHORUS BLOOD SERUM DETERMINATION

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BLOOD serum calcium and inorganic phosphorus determination is a part of our routine examination in patients in whom such findings might be of value. Among those in whom such examinations were made were forty-eight patients with defective teeth.

The Kramer Tisdall method was used for estimating blood serum calcium and the Benedict Thoms method for estimating inorganic phosphorus.

In this group there were twenty four males, twenty four females

<i>Age of Patients</i>		<i>Physical Condition</i>
Under 5 yr	23	Good in 25
5 to 10 yr	21	Fair in 21
10 to 15 yr	"	Poor in 2

If we look upon 9 mg of calcium in 100 c.c serum as the low normal for children forty six of these patients had normal serum calcium. In a boy thirteen years old the calcium was slightly lowered, 8.936 mg a boy ten years old showed 8.964 mg calcium both practically normal.

If the normal phosphorus content is considered as from 4 to 6 mg in 100 c.c. serum the phosphorus was normal in all. These patients were not children with a filled cavity or two but they had gross lesions as is evidenced by the fact that they were referred to us by dentists and family physicians for calcium determinations. It is evident that in these children there were present factors for the dental caries other than the calcium and phosphorus content in the blood serum, which serves simply as a transportation medium between the gut and the osseous system and from there to the kidney and gut for excretion.

The vast amount of literature accumulated during the past few years as to the etiologic factors in dental caries in children is characterized by the positive opinion and frank disagreement of the various authors. Our clinical observations of many hundreds of children in whom appraisal of the dental condition has been included in the examination lead us to believe that nutritional agencies dental hygiene bodily disorders both acute and chronic—play a rôle important but secondary to a fundamental constitutional error as a cause of dental caries. Again from the clinical point of view two diseases of children show pronounced dental defects as a part of their symptom-complex. The tooth condition is an outstanding feature of the stigma and is in itself diagnostic in those conditions. We refer to syphilis (congenital) and hypothyroidism (cretinism). These are two constitutional disorders in children in which

the teeth rarely escape involvement and in each disease show characteristic pathologic manifestations. All are familiar with the bony changes in congenital syphilis. Osteochondritis and dactylitis are observed as early as the third month of life in many instances, and time and again Hutchinson's teeth have been the only suggestion of congenital syphilis in a patient during an examination, and corroboration of the diagnosis of syphilis being proved by a four-plus Wassermann reaction.

In the cleft the teeth usually show delay in eruption and invariably a gross pathology at later periods. Engelbach¹ writes as follows: "Among forty-three cases of juvenile thyroipituitarism eighteen showed orthodontic changes such as overcrowding, malposition, defective calcification with decay of the teeth."

The family history of dental caries carries with it the suggestion of a constitutional ailment. In the vast majority of parents of children with carious teeth, inquiry and examination showed the child was carrying on the familial defect. When a group of children show a profound selective pathologic tooth condition of a known etiology, as in the case of syphilis and hypothyroidism, it is logical to assume that a lesser manifestation of the stigma might be a sensitive index, perhaps the remotest indication of the disability and without other signs of physical derangement. In this connection it is fair to assume that caries in the young may be due in part to a systemic deficiency with failure to produce and maintain a tooth structure capable of resisting the various agencies that may prove destructive.

It is our belief that dental caries may be prevented in many children through recognition of defects in the parents and the introduction of replacement measures at the onset of pregnancy. When the thyroid gland is better understood, it will be found that it possesses possibilities of varying functional capacity under varying conditions of bodily vigor. We have demonstrated in our study, "Fatigue in School Children,"² incident to social demands, school activities, and adolescence, that there may be a temporary inability of the thyroid gland to meet the demands placed upon it, as demonstrated by means of the basal metabolism test, the blood pressure, and functional cardiac manifestations. This observation was further corroborated therapeutically through the administration of the desiccated thyroid gland. It is not beyond the bounds of reasonable conjecture that gravidity with its demands upon the female might call for a greater thyroid hormone supply than the individual can furnish with the resulting characteristic remote effects upon the child, both antenatal and postnatal.

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ENCEPHALITIS AND MYOCARDITIS IN A FATAL CASE OF TRICHINOSIS

REPORT OF A CASE IN A FOURTEEN YEAR OLD GIRL

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THE present case of trichinosis is reported because of several interesting points (1) the predominance of a picture of encephalitis throughout the entire course, (2) the absence of three generally accepted diagnostic criteria: gastrointestinal symptoms, muscular tenderness and eosinophilia until the day preceding death, (3) death of the fourteen year old girl, and (4) changes in the brain and myocardium found on postmortem examination.

Six individuals, five adults and one girl fourteen years old, had eaten pork sausages on Jan. 21, 1934. Within a few hours to a few days the members of the group complained of symptoms which were considered as influenza as manifested by general muscular pains, fever, headache, abdominal pains and weakness. Four of the group made uneventful recoveries at home. The girl who was admitted to a hospital, is the subject of this report. The brother was admitted to the Israel Zion Hospital on the day preceding her death. He ultimately recovered but presented a picture of transitory encephalitis for two days after admission. Trichinae were found in his deltoid muscle on biopsy.

We have been able to obtain a record of the eosinophile count and of later blood counts in some of the group.

The meat had been obtained from the same butcher with whom the family had been dealing for many years, and it bore the stamp of inspection of the United States government. The sausages were prepared from the pork dried and suspended by the family. We understand that they were then fried before being eaten.

CASE REPORT

H. M., fourteen years old, became ill with what was considered to be the grip manifested by high temperature, sore throat, joint pains, and general soreness. The condition became aggravated, the fever continued and eight days after the onset edema of the eyes appeared. She was admitted to the Israel Zion Hospital on the twelfth day of her illness. For the previous two days she had been in another hospital where her condition had been diagnosed as influenza complicated by acute nephritis.

From the Departments of Pediatrics and Laboratories, Israel Zion Hospital.

of the mucosal folds. The rest of the small intestine was slightly dilated. Dark blue hemorrhagic areas 0.5 cm in diameter were scattered throughout the serosa. There was a dirty grayish green fibrinous exudate near the terminal ileum with some congestion of the serosa.

Microscopic Findings—(Stained with hematoxylin eosin.) Brain. Sections from parietal lobe showed that the pial membrane was slightly thickened with a sparse

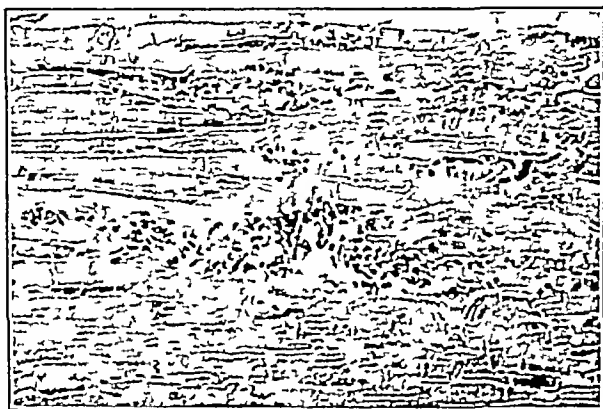


Fig 2—Trichinous myocarditis with focal cellular infiltration ($\times 100$)

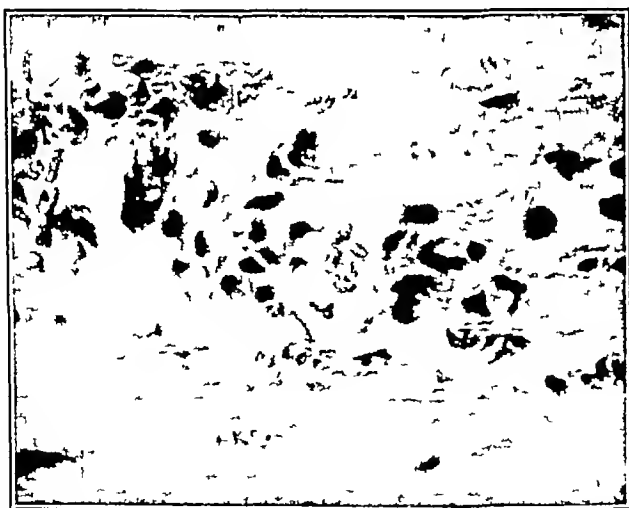


Fig 3—High power magnification of field shown in Fig 2. Focal destruction of muscle fibers with mononuclear collection. One large macrophage is seen ($\times 450$)

infiltration of mononuclears and an occasional macrophage. Infrequently the cortical cells revealed slight nuclear chromatolysis. The Virchow Robin spaces were slightly widened. The glia cells were slightly increased in number, this was most noticeable in the vicinity of the capillaries. All cortical capillaries were immensely engorged and prominent throughout. Some interstitial edema was present in all sections.

Heart. Distinct interstitial infiltrations, focal in character, were noted throughout, a number were perivascular in location. The majority of the cells were

histiocytes with numerous mononuclears and an occasional neutrophile. The adjacent muscle fibers were disrupted and frequently disintegrated. A number of the cellular foci showed red cell extravasation. The muscle fiber striations as a rule were well preserved. Careful study of numerous serial sections from several blocks failed to disclose the presence of trichina larvae.

Skeletal Muscle The muscle fibers throughout the diaphragm were the seat of cloudy swelling and occasional hydropic degeneration, with numerous areas showing coagulation necrosis. There was a rather widespread interstitial cellular infiltration in focal collections for the most part. The cells consisted of approximately equal proportions of neutrophiles, mononuclears with abundant, sometimes ameboid basophilic cytoplasm and macrophages containing engulfed red cells with degenerating nuclear remnants or vacuoles.

In the center of a number of these cell clusters were noted sections of the trichina larvae the adjacent muscle fibers were in various stages of degeneration. The larvae were surrounded by a pseudolining of flattened mononuclear cells enclosing a slightly granular pink staining substance. Not infrequently multinucleated giant cells were located at one pole of the encapsulated lesions. Appreciable fibroblastic proliferation was not seen. Additional sections from the psons and abdominal muscles revealed essentially the same inflammatory myositis, with distinctly less cellular infiltrations and only an infrequently encountered trichina larva.

COMMENT

Case reports of trichinosis in children are fairly frequent in the literature. In the series of van Cott and Lintz² four of the ten affected were children as were eight of the eleven in the report of Reifenstein and his coworkers³. One of the patients in the former series nursed her infant throughout the entire course until she was incapacitated but the infant remained well. The authors considered this as evidence that trichinae are not transmitted through maternal milk and that a nursing mother does not infect her nursing. On the other hand, Salzer⁴ reported the finding of trichinae in mother's milk and in excised mammary tissue.

There is a general tendency to consider the disease a mild one in children both as to morbidity and mortality. The death rate in children is less than the overage of 5.6 for all ages. The mildness of the disease in children is due to the probability that they eat less meat and thereby ingest fewer trichinae. McCoy⁴ noted experimentally a mathematical relationship between the amount of ingested meat and the severity of the disease. Other factors are considered by some to be responsible for the mild course in children. 1 Weakness of the gastric juices which interferes with liberation of the encapsulated trichinae. 2 Expulsion of large amounts of undigested particles of infected meat in the frequent bowel movements. 3 Shortness of the gastrointestinal tract. These reasons are probably more speculative than conclusive.

The symptoms may be divided into three stages which are more or less defined and manifest clinically the life history of the parasite. The stage of intestinal infestation may occur in a few hours or several

days after the ingestion of the meat. This is followed by the stage of dissemination in which the embryos invade the lymphatics and blood stream and attack the muscles. Trichinae have been found in spinal fluid, blood, feces, maternal milk, mammary tissue, and in other regions. The stage of regression or encystment of the larvae begins at about the end of the fourth or fifth week.

The manifestations are continued fever, muscle pains, especially of the gastrocnemius and biceps, abdominal pains, and diarrhea. Pepper⁵ stated that diarrhea is more marked in children and may be a probable explanation of the mildness of the cases in this age group. It is interesting to note that in our fatal case there was an absence of diarrhea and severe gastrointestinal symptoms. Marked edema of the face, especially about the eyelids, is a prominent symptom, and is considered by some to be due to occlusion of the local capillaries by the embryos. The picture may simulate muscular rheumatism, typhoid fever, gastroenteritis, encephalitis, and meningitis.

A number of observers have noted the preponderance of meningitic and encephalitic symptoms. Meyer⁶ reported three instances in children in whom diagnoses of cerebrospinal meningitis had been made upon the strength of neck rigidity, positive Kernig sign, absent knee jerks, delirium, irritability, and photophobia. The spinal fluids were all clear and showed on cytologic examination from 40 to 240 cells to the cubic centimeter. Trichinae were found in one case. Pund and Mosteller's⁷ patient was an eleven-year-old girl in whom symptoms of encephalitis occurred three weeks after vaccination against small-pox. Walker⁸ noted a meningitic picture in a boy after the ingestion of bear meat which was later found to be loaded with trichinae. Van Cott and Lintz were the first to obtain the trichinae from the spinal fluid of a patient who presented symptoms and signs of acute meningitis.

Pund and Mosteller reported four instances in the literature, in addition to their own case, in which trichinae were present in brain tissue. Bloch and Hassin⁹ reported microscopic findings in the brain, which consisted of rather sparse lymphocytic infiltration, perivascular vacuolization, and marked capillary congestion. We were able to note a similar diffuse degenerative action, obviously nonspecific. We are in accord with the viewpoint of Gruber and Gamper¹⁰ that central nervous system changes in trichinosis are analogous in nonspecificity to those found in the brains in cases of malaria, typhoid fever, and other systemic infections.

The number of larvae in the brain, even after scrutinizing search, does not approximate that found with greater ease in striated muscles. Cellular inflammatory response in nervous tissue as manifested by leucocytic and glia cell collections or focal hemorrhages is undoubtedly due to the transient presence of parasites in the brain.

There is a discrepancy between the clinical picture of encephalitis and the paucity of severe organic changes in the brain in Case 1. We cannot estimate to what extent the mild microscopic inflammatory changes are responsible for the symptomatology. The slight meningeal reaction noted both clinically and histologically does not compare with the definite clinical pictures observed by Gruher and Gramper¹⁰ Knorr¹¹ and Chasanow¹². It is interesting to note that even these observers failed to find a definite relationship between the degree of tissue destruction and the severity of the clinical reaction.

Larvae of trichinosis were first demonstrated in heart muscle by Zenker¹³ in 1860. Though we were unable to find any even after diligent search in several hundred serial sections we observed a rather widespread focal myocarditis. Several investigators state that the cellular myocardial reaction is due to the previous presence of the larvae during the invasive stage. Degenerative and exudative myocarditis have been noted by several observers.^{7, 10, 14, 15} Zoller¹⁶ and Dunlap and Weller¹⁷ observed the larvae of trichinosis in the heart muscle of experimental animals as early as the fifth day after infestation. The irritative cellular response evoked by their presence outlasted their emigration for permanent quarters in skeletal muscle a few days later. No larvae could be found in the animal's heart muscle after the second week.

Eosinophilia as a diagnostic criterion has been stressed by Brown¹⁸ Adam¹⁹ Chasanow¹² and by others to such an extent that it has assumed a *sine qua non* position in the diagnosis of trichinosis. Brown's original case showed an eosinophilia of 68.2 per cent. Reifenshtein and his associates² found an average of 24.5 per cent in their series. Others feel that eosinophilia is not a constant or invariably dependable finding nor is the degree of eosinophilia a criterion of the severity of the disease. It may be absent throughout the entire course or may not appear until the convalescent stage. Reifenshtein and his associates, on the basis of an extensive review of the literature, stated that cases which fail to exhibit eosinophilia throughout the entire acute stage are to be regarded as those in which recovery is unlikely. Pepper and others have also noted the absence of eosinophilia in severe and fatal cases. These observations are confirmed to a great extent by the findings in our case which did not show any eosinophilia until twenty-four hours before death. Marked eosinophilia was present in the blood of the other three patients in our group in the acute stage. It is interesting to note that in the brother no eosinophiles were found in the admission examination. The eosinophilia subsided with the acute stage in two of the three patients and was still present in one (the father) six months later.

New diagnostic approaches in trichinosis have been indicated by Bachman²⁰ who recently has described a precipitin reaction and an

intradermal test The few experimental and clinical studies which have been reported^{21, 22, 23} are inconclusive as to their values The consensus of opinion seems to be that the skin test is of more practical application but that it is of limited aid in the first few weeks of the illness

Any measures which will aid in earlier diagnosis will make possible more efficient treatment The latter should have for its object the expulsion of the trichinellae and the killing of the young larvae before they get into the blood stream The most opportune time would be in the gastrointestinal stage and may be accomplished by catharsis and an helminthic like hexylresorcinol or thymol

In the hands of Salzer³ human convalescent serum gave beneficial results Almost complete prophylaxis was obtained in animals which had previously been fed infected meat Beneficial results were also obtained in human subjects as indicated by the temperature, eosinophilia, and general course of the disease The injection of nonimmune serum and salvarsanized serum did not give the same results Nieto,²⁴ however, reports prompt recovery after three intravenous injections of neosalvarsan (0.015 gm for every kilogram of body weight) Schwartz and Alexander²⁵ did not succeed in obtaining any of the beneficial results with convalescent serum reported by Salzer

Riley and Scheffley²⁶ suggested the extension to small plants of the federal regulations regarding the preparation of sausage and other pork products which are ordinarily consumed without being cooked They also call attention to the fallacy that government-inspected pork is free from trichinae Microscopic examination for trichinae was discontinued by the government in 1907, and there is no attempt to carry out any such examinations at the present time in any part of the United States The best form of prophylaxis is adequate cooking of pork products prior to consumption It would be best to eliminate all pork products from the dietary of children

SUMMARY

A fatal case of trichinosis is reported in a fourteen-year old girl who presented a predominating picture of encephalitis throughout the entire course Three generally accepted diagnostic criteria of the disease were absent gastrointestinal symptoms, muscular tenderness, and eosinophilia (until the day preceding death) On postmortem examination myocarditis, cerebral congestion and edema, and toxic encephalosis were found Studies of the diaphragm, psoas, and rectus abdominalis disclosed heavy infestation by the parasites in the early stages The brain findings were scant in proportion to the pronounced clinical picture of encephalitis Blood studies in five individuals affected at the same time are presented Trichiniasis of the right deltoid was found in a brother who presented a transitory encephalitic picture and recovered

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A CLINICAL AND CHEMICAL STUDY OF NONDIABETIC KETOSIS WITH ACIDOSIS

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ALTHOUGH many studies¹ of ketonuria in nondiabetic children have been reported, no studies reveal the effect of nondiabetic ketosis on the serum electrolytes. This paper reports electrolyte studies on twenty patients with nondiabetic ketosis. Since the study includes only such patients presenting symptoms suggesting acidosis, only three failed to reveal appreciable reduction of serum bicarbonate. The latter are included since they probably exhibit the typical chemical changes in the blood produced by mild ketosis demanding but little special treatment. The other patients probably represent the types of cases with acidosis associated with nondiabetic ketosis which enter the pediatric wards of a hospital.

Methods—The electrolyte determinations were all carried out on venous serum by the following methods: ² bicarbonate, Van Slyke and Neill, chloride, Van Slyke, protein, macro Kjeldahl, total base, Stadie and Ross, sodium, Barber and Kolthoff, phosphorus, Benedict and Theis,³ and potassium, Hald's modification of the method of Shohl and Bennett.⁴ Blood sugar was determined on a Somogyi⁵ precipitate by the method of Shaffer and Hartmann.² A slight modification of the method of Scott Wilson⁵ was used to determine acetone. One cubic centimeter of concentrated sulphuric acid was added to a protein free filtrate of either whole blood or serum and the acetone distilled into Scott Wilson reagent. The mercurial precipitate was separated by centrifugalization and washing with water and centrifuging again. The precipitate was then dissolved in a mixture of HNO₃ and H₂SO₄, oxidized by heating and titrated with N/20 NH₄SCN, using solid ferric ammonium chloride as an indicator. The method is only approximate with the quantities used (equivalent to 1/2 to 1 c.c. of blood), the error being about 20 per cent. The results are reported as quantitative since in most cases the approximate result was all that was needed for understanding the acid base balance, and more accurate results would have required more blood than would have been available if the other studies were carried out simultaneously.

CLINICAL ASPECTS OF THE CASES OF NONDIABETIC KETOSIS

Since previous studies have been carried out largely on cases of so called "recurrent vomiting," it is desirable to present a short analysis of the material from a clinical point of view. Brief case histories are given in the appendix, but the chief points to be emphasized are summarized in Table I.

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TABLE I
CLINICAL ASPECTS OF CASES OF KETOSIS

CASE	SEX	INFECTION	AGE (YR.)	OUTCOME	W.B.C. THOUSANDS PER CMM.	TEMPERATURE (C.)	LIVER SIZE	ACIDOSIS
<i>Cases With Minimal Infection</i>								
1	M	Recurrent vomiting (A)	1.2	R	33	37.8	++	++
1	M	Recurrent vomiting (B)	1.2	R	6	37.5	++	++
2	F	Recurrent vomiting	3.5	R	12	37.5	0	+
3	M	Recurrent vomiting	4.0	R	10	37.5	+	0
4	M	Isolated attack of ketosis	1.2	R	9	38.0	++	++
5	M	Isolated attack of ketosis	5.5	R	5	38.0	0	+
6	M	Methyl salicylate poisoning	2.0	R	10	37.5	+	+
7	F	Newborn encephalopathy		R	18	37.5	+	++
<i>Cases With Moderate Infection</i>								
8	M	Alimentary anemia, pharyngitis	2.0	R	32	40.0	++	+
9	M	Congenital heart disease	8.0	R	9	38.0	++	+
10	M	Isolated attack of ketosis	2.5	R	10	38.0	0	+
11	M	Bronchitis	4.0	R	15	37.5	0	0
12	F	Bronchitis	5.0	R	11	39.0	0	0
13	M	Bronchiolitis	5.0	R	17	39.0	0	0
<i>Cases With Severe Infection</i>								
14	F	Pneumonia	2.5	R	45	40.0	±	+
15	M	Scarlet fever, mastoiditis	2.5	R	19	38.5	++	++
16	M	Scarlet fever septicemia	4.0	R	15	40.0	++	+
17	M	Enterococcal septicemia, peritonitis	1.0	D	18	40.0	++	++
18	F	Bronchiolitis, bronchopneumonia	0.9	R	19	40.0	++	++
19	F	Sepsis neonatorum (<i>Str. Aem.</i>)		D	†	37.8	++	++
20	M	Undiagnosed	0.8	D	25	37.5	++	++

Seven cases showed few or no evidences of infection. Although the same patients might be considered to suffer from moderate infections by some physicians, observation of the course in the hospital never revealed serious infections and such evidences of infection as were found on admission may be interpreted otherwise. Since a red pharynx is characteristic of practically all patients suffering from acidosis and dehydration particularly when vomiting occurs, this finding was disregarded unless it persisted after the acidosis was relieved. Similarly leucocytosis and slight transient fever were regarded as manifestations of dehydration in patients who otherwise showed no manifestation of infections.

The cases with minimal evidences of infection included three cases of "recurrent vomiting" and two cases with isolated attacks of vomiting and ketosis which seemed similar to the attacks which recurred

Case 10 probably also belongs in this group, but evidences of infection were so definite that it was placed in the group suffering from moderate infection

Attention is called to Case 6 (methyl salicylate poisoning) since it represents the only case in which no vomiting occurred. The patient was lavaged in the hospital about three-quarters of an hour after swallowing about one-half ounce of oil of wintergreen. Since ketosis has been reported in poisoning with methyl salicylate,⁶ the child was kept in the hospital despite the fact that he appeared well. He was given 500 c c of physiologic saline solution subcutaneously and 200 c c of 10 per cent glucose intravenously. Despite this treatment, clinical and chemical evidence of mild ketosis with acidosis was found eighteen hours later.

In Case 7 a severe ketosis developed in a newborn infant following vomiting, inability to take water and food by mouth, and severe dehydration. At six months of age the patient was spastic, microcephalic, and markedly deficient in mental development. The cause of the defective development of the brain might conceivably have been a cerebral injury at birth, but the symmetrical nature of the lesions indicated that a developmental defect or cerebral degeneration was more likely. The case brings out the fact that severe ketosis can occur in newborn babies (see also Case 19).

The six cases with moderate infection are of little interest since they showed but mild ketosis and acidosis. Since in these patients vomiting was quite severe in all but one (Case 9), they illustrate that marked vomiting alone does not produce severe ketosis. In Cases 9 and 10 the patients suffered from mild upper respiratory infections.

The seven cases with severe infection are of especial interest since they show the importance of recognizing that ketosis can play a prominent rôle in some infections. While the infections probably played the chief rôle in the illnesses, successful treatment of the ketosis and acidosis undoubtedly was responsible in large measure for the favorable outcome in certain cases (Cases 15, 16, and 18). Although three cases were associated with infections due to hemolytic streptococci (Cases 15 and 16, scarlet fever, and Case 19, sepsis neonatorum), such factors as vomiting and age seemed to play the chief rôle in the development of ketosis rather than the type of invading organism. In Case 16, it was striking that ketosis persisted as long as the liver remained large, despite administration of intravenous glucose.

The effects of ketosis did not apparently lead to the fatal outcome in Cases 17, 19, and 20. In Case 17, the patient suffered from enterococcal peritonitis and sepsis, and in Case 19, from streptococcal sepsis and encephalitis. Although the cause of death was not determined in Case 20, chemical and clinical evidences of ketosis, acidosis, and dehydration were absent at the time of death. However, the patient re-

mained in coma and shock and a terminal rise in temperature to 40 C occurred. The clinical course suggested encephalitis although the negative blood cultures do not entirely exclude an overwhelming bacterial infection.

The ages of the patients are of especial interest. Two were newborn infants who suffered from cerebral disorders. Four were under one year of age and ten under two. Of the nine admissions during which the serum bicarbonate was found to be below 11 milliequivalents per liter (26 volumes per cent), seven were younger than fifteen months, and the other two were aged two and one half and four years, respectively. *Ketosis with acidosis apparently is more frequent and severe in infants younger than a year and a half.*

Of the nineteen patients, only five were girls. While the series is small, the preponderance of males may represent a significant difference rather than a chance selection of cases. The literature reveals about an equal distribution between boys and girls in recurrent cases.

Fever was absent or slight except in the presence of infection. Leucocytosis over ten thousand unrelated to obvious infections occurred only three times. In Case 1 A and Case 7 the leucocytosis was presumably related to severe dehydration. Since comparatively mild infections often lead to marked leucocytosis in cases of alimentary anemia, the high count in Case 8 was probably associated with the infection and anemia rather than with the ketosis, acidosis and dehydration.

Enlargement of the liver* was striking in this series of patients. Only Cases 2, 5, 6 and 10 failed to show enlargement of the liver in the presence of well-developed ketosis. In Cases 11, 12 and 13 the liver was not enlarged but these patients can hardly be considered examples of severe ketosis. The enlargement of the liver was apparently not related to cardiac failure except perhaps in the patient with a congenital lesion of the heart (Case 9). Although circulatory failure was undoubtedly present in the patients who were markedly dehydrated it does not seem likely that the circulatory failure accompanying dehydration leads to enlargement of the liver since a similar grade of dehydration in diarrhea is not accompanied by enlargement of the liver. None of the patients was jaundiced and, while the icteric index was not determined, abnormal pigmentation of the serum was not observed when making chemical analyses of the serum. The bloods from two patients with catarrhal jaundice failed to reveal significant ketosis.

ACID-BASE BALANCE OF THE SERUM

Table II gives the results of the analyses of blood.

In estimating enlargement of the liver due consideration was given to variations in the relative position of the liver in normal infants and children of various ages. In all patients thought to have enlarged livers, the size decreased during convalescence. In Case 19 the enlargement was demonstrated at autopsy.

TABLE II
CONCENTRATION OF SERUM ELECTROLYTE, BLOOD SUGAR AND N P N

CASE	DATE	'HCO ₃ ' MEQ PER L	'CL' MEQ PER L	PROTEIN MEQ PER L	"HPO ₄ " 'HPO ₄ ' MEQ PER L	'ACETONE' MEQ PER L	NA+ MEQ PER L	K+ MEQ PER L	TB+ MEQ PER L	SUGAR MG PER CENT	N P N MG PER CENT	PROTEIN GM PER CENT
1 A	10/27/29	59	117.4	20.0	2.5	8.0			160.0		36	8.09
1 A	10/28/29	19.7	123.4	15.7	1.8	8.0			178.9		30	6.40
1 A	10/30/29	36.8	101.4	12.8					154.6	97+	20	5.17
1 A	11/1/29	31.8	102.8	15.3	1.4				157.0	81+		6.20
1 A	11/6/29									97+		
1 B	11/16/29*	6.35	106.4	16.3		10.8			156.4			6.58
1 B	11/17/29	14.1	113.4	15.1		2.4			150.9			6.09
1 B	11/20/29	26.9	100.8	16.8					151.0			6.81
2	2/22/33*	13.8	99.7	17.3	2.8	+			138.3	52+		7.2
3	10/31/29*	23.5	107.5	16.8	1.6	2.0				97+	44	6.6
3	11/5/29									109		
4	9/14/30*	6.34	103.0	16.5		11.5			146.8	62+		6.66
4	9/15/30	12.1	104.2	14.8	2.7	4.1			149.2	185		5.83
4	9/17/30	19.0	99.6	14.4		3.4			149.4	116		5.82
4	9/23/30					0.9				107+		
4	8/3/34*	15.7	99.0	18.6		5.9			147.0	48+		7.51
5	8/26/32	13.01	108.4	15.7	3.6	4.8			142.6		31	6.48
6	12/23/31	7.1	121.3	15.8		14.9			152.0	143	35	6.40
7	12/24/31	15.4	116.0	14.2		2.8			152.0	86+		5.75
7	12/28/31	22.5	103.8	12.5					151.6		43	5.05
8	7/31/32*	15.5	100.7	15.6		4.7			147.0	67+		6.44
8	8/1/32	19.6	99.3	16.3		2.3			147.2	105+		6.80

TABLE II—Cont'd

CASE	DATE	HCO ₃ M.EQ. PER L.	CL M.EQ. PER L.	PROTEIN M.EQ. PER L.	H ₂ PO M.EQ. PER L.	ACETONE M.EQ. PER L.	NA ⁺ M.EQ. PER L.	K ⁺ M.EQ. PER L.	T.B.+ M.EQ. PER L.	SUGAR MG PER CENT	N P X MG PER CENT	PROTEIN GM. PER CENT
8	1/10/32	14.8	100.0			10.6			144.4	87†		6.25
9	1/18/32	28.8	99.5						155.0	65†		6.85
10	8/10/30	12.0	109.0	17.1		8.0			146.8	108†	27	6.44
10	3/11/30	10.9	108.2	15.9		2.8			139.8			6.01
11	5/19/30	19.3	103.0	14.4					146.6	58†		6.88
12	4/22/30	19.9	101.6	15.8	1.9	1.9	131.8	8.0		89†	84	8.24
13	8/15/32*	17.7	102.8	20.4	2.0	2.0	129.0	2.6		176†		7.4
14	8/9/34	15.6	90.0	18.0		7.8	137.5			189†		8.7
15	4/8/32	11.3	85.9	21.6						65†		
15	4/13/32									110	55	4.78
16	8/5/30	10.8	101.0	12.2		6.1			180.5	00†	28	5.70
10	8/7/30	15.1	99.2	13.8		5.5			184.8	87†	19	5.09
10	3/11/30	29.7	101.2	11.9		0.0			102.8		120	5.31
17	2/15/30	10.1	104.4	12.7	4.4	3.7			140.0		60	7.64
18	12/7/32	5.1	123.9	18.9	8.2	4.5	157.6	8.1	149.0	102†	82	5.74
18	12/8/32	10.8	115.8	14.3		4.4	138.2	8.1		400		5.40
18	12/9/32	19.1	105.1	13.4		8.0			150.3	163		6.68
10	1/10/38	7.7	109.1	10.5		7.0			158.4			4.42
19	1/21/38		117.6	10.9		5.8			163.4	200		6.81
20	10/4/30	5.4	100.0	18.8	2.4	4.2			147.4	133	84	5.50
20	10/6/30	21.0	98.8	14.0		0.9						

Bloods taken without treatment, such as hypodermoclysis, which might alter the concentration of serum chloride and bicarbonate.

†Bloods taken at least six hours after feeding or infusion of glucose.

While blood sugar was not determined on admission in all cases, a sufficient number was obtained to demonstrate that the concentration of blood sugar in cases of severe nondiabetic ketosis seldom differs significantly from that of other hospital patients. In Cases 2, 4, 5, 8, 10, and 11 the values are somewhat low, but not below that found frequently in fasting children. In Case 15, the blood sugar content was so high that diabetes was suspected even though the patient did not strongly suggest the diagnosis clinically. Subsequent determination of the sugar tolerance to intravenous glucose revealed a normal reaction.

The reduction in serum bicarbonate was as great in these patients as one is accustomed to meet in diabetic coma. As pointed out previously, the marked reduction in bicarbonate occurs chiefly in the patients aged less than fifteen months. In most cases the diminution of bicarbonate is only partially explained by accumulation of ketone acids. Increase in chloride was considered in Cases 1 A, 7, and 18. In Case 1 A, the high chloride (117.4 m eq per liter) is only partly explained by the hypodermoclysis of 400 cc of physiologic saline about eighteen hours before the blood examination. In Case 7 (121.3 m eq per liter), a hypodermoclysis of 250 cc of saline was given about twelve hours previously. Since intravenous infusions of glucose were given in all cases, the elevation of chloride is probably not explained by the hypodermoclyses. In Case 18 no saline was given before the blood analysis, but the high chloride (123 m eq per liter) may be explained by the diarrhea. In Case 15, the chloride was low (85.9 m eq per liter).

The concentration of total base was normal in most of the cases, but tended to be reduced in the patients with severe infections. In Case 16, the reduction in total base was considerable (130 m eq per liter).

In many of the cases the concentration of acetone was only moderately elevated, but high values were found in Cases 1 A, 1 B, 4, 5, 6, 7, 9, 10, 15, 16, and 19.

The high nonprotein nitrogen in Cases 16 and 18 is probably referable to dehydration and oliguria.

Considerable concentration of the blood was indicated by the initial concentration of serum protein and its subsequent fall in Cases 1 A, 1 B, 4, 7, 18, 19, and 20. A gain in weight during recovery indicated that the loss of fluid was not confined to the plasma. However, the gains in weight, except in cases 1 A, 1 B, 7, 15, 18, and 20, were not as great as one is accustomed to find in alimentary intoxication.

In summary, the chemical findings of the blood reveal dehydration and reduction of bicarbonate due to accumulation of ketone bodies and in some cases to increased concentration of chloride. If one considers the loss of body fluid indicated by the loss in weight and the diminished

skin turgor, the patients must be deemed to suffer from deficit of sodium, chloride and water in about the proportion they occur in the blood plasma. The blood sugar gives no direct evidence of the nature of the disturbance in carbohydrate metabolism except that it is not like that of diabetes mellitus.

RESULTS OF TREATMENT

The general plan of treatment of these patients was as follows: (1) Vomiting was minimized by withholding water and food by mouth as long as nausea was present or vomiting seemed likely to occur. Water or water with glucose was often given in small amounts (from 15 to 30 cc every fifteen to thirty minutes) when it was felt larger volumes might induce vomiting. (2) Deficit of water and electrolyte was restored by hypodermoclyses of physiologic saline or alkaline saline solutions.^{1, 2} In some cases proteolyses were also used. (3) Intravenous infusions of glucose solutions were given to promote oxidation of glucose and to restore any possible deficit of available carbohydrate in the body. In most cases these procedures were considered sufficient to lead to recovery from dehydration, acidosis, and ketosis. However, in certain cases sodium bicarbonate was given by mouth when acidosis seemed so severe as to make it seem necessary to obtain prompt recovery of serum bicarbonate. In some cases insulin was administered in conjunction with glucose on the assumption (probably erroneous) that oxidation of glucose might be accelerated.

No systematic evaluation of the results of treatment can be given because of the heterogeneous character of the cases. Nevertheless, certain impressions concerning treatment can be brought out.

The recovery of the normal electrolyte pattern was quite prompt in most of the patients as evidenced by subsequent examinations of the blood and by the clinical course. In twenty-four hours clinical improvement was marked and the bicarbonate increased considerably but seldom reached normal values until treatment had been carried out for forty-eight hours. Attention is called particularly to Cases 1 A, 1 B, 4, 7, 18, 19 and 20 in which the greatest reductions in bicarbonate were found.

Sodium bicarbonate was given by mouth in Cases 1 A, 1 B, 16, and 18. In Case 1 A 10 gm divided in three doses was given between the first and second examinations of the blood. The child gained in weight from 10.1 to 10.8 kg and the concentration of serum protein decreased from 8.09 to 6.40 per cent. The serum bicarbonate increased from 5.9 to 19.7 m.eq. per liter while the chloride increased from 117.4 to 123.4 m.eq. per liter and the ketone bodies remained the same. In other words the recovery of serum bicarbonate was accomplished by the administered sodium bicarbonate while the remaining electrolyte remained about the same except for the increased volume of body fluid.

indicated by the gain in body weight. The third blood sample shows that oxidation of the ketone bodies freed enough sodium for combination with carbon dioxide to raise the level of serum bicarbonate to 36.8 meq per liter. No untoward symptoms accompanied this alkalosis, but reduction of serum bicarbonate was slow as is seen in the fourth sample taken a day later. A slightly high serum bicarbonate also resulted in Case 16 when sodium bicarbonate (2 gm daily from March 7 to 11) was given by mouth. In Cases 1 B and 18, no alkalosis developed following the administration of 25 and 20 gm of NaHCO_3 by mouth. While no harm was done in these cases, we feel that sodium bicarbonate is probably seldom if ever indicated in nondiabetic ketosis with acidosis. The use of alkaline saline or Hartmann's solution^{7, 8} subcutaneously probably is somewhat more effective than physiologic saline. In any case subcutaneous saline solutions should be given in sufficient amounts to induce a diuresis. The slow recoveries in Cases 1 A and 4 were thought to be due to administration of inadequate amounts of saline solutions.

In Cases 1 B, 2, 4, 15, and 16 insulin was given in conjunction with infusions of glucose. The more rapid recovery in Case 1 during the second than the first admission was thought to be due to the prompt administration of an adequate amount of saline rather than the effects of insulin. In Case 16 insulin and glucose were given over a period of three days before the acetone of the urine decreased appreciably. Since we are accustomed to obtain more prompt results in diabetes, insulin does not seem to give the good results one obtains in true islet deficiency. The other cases in which insulin was used responded in much the same manner as the cases in which it was not used. The absence of hyperglycemia indicates that the use of insulin is irrational and unnecessary.

DISCUSSION

The group of cases of nondiabetic ketosis with acidosis presented in this paper brings out a number of factors, which, though not new, deserve more attention than has been given in the literature. Although ketonuria has been known to accompany a number of infections and other unrelated disorders, it is usually not appreciated that cases of marked acidosis are more frequently met in isolated attacks than in recurrent episodes. Since attention has been centered chiefly on cases of recurrent vomiting, the high incidence and severe character of ketosis in children younger than a year and a half is hardly mentioned in the literature.⁹⁻¹⁰ Gee¹¹ and others call attention to the fact that recurrent vomiting may start in infancy. Ketosis with acidosis in newborn infants has not been reported previously.

The frequency with which normal or high concentration of serum chloride was found in these patients is hard to explain if one assumes

that the vomitus contains normal gastric juice. Unfortunately the vomitus was not analyzed except in Case 3. This vomitus showed a normal excess of chloride over fixed base, but this finding may not be typical of ketosis with acidosis since this patient did not suffer from acidosis. During convalescence the gastric juice was normal on both admissions in Case 1. Knoepfelmacher¹² reported that the vomitus was acid early in the course of an attack of recurrent vomiting but later showed no free hydrochloric acid. O. Schloss found the vomitus to contain an excess of fixed base over fixed acid in some unpublished observations. The chemical findings in the serum indicate that patients showing ketosis with acidosis will probably frequently be found to vomit an alkaline juice.

Since it is appreciated that when fat is burned without a simultaneous combustion of carbohydrates ketosis develops, the theories of the pathogenesis of nondiabetic ketosis have centered about available carbohydrate of the body. Solomonson¹ summarized the work on recurrent vomiting and performed carefully controlled experiments of his own. He pointed out that, while starvation or a diet high in fat and low in carbohydrate tends to produce certain symptoms resembling an attack of recurrent vomiting the fully developed picture has not been reproduced. These procedures were followed in some cases by vomiting, slightly enlarged liver, lowering of the blood sugar, and an increase in blood acetone but the symptoms were never as severe as those of clinical cases. Similar induction of symptoms resembling those of recurrent vomiting have been reported by a number of workers.¹²⁻¹⁷

Ross and Josephs¹⁶ noted an unusually low blood sugar content during a convulsion in a child subject to attacks of recurrent vomiting. Josephs¹⁷ confirmed and extended the observations and brought out that certain children develop a greater lowering of their blood sugar after fasting for sixteen hours than others. However subsequent observations^{18, 19} showed that starvation in normal children produces fairly marked lowering of the blood sugar and that this hypoglycemia is not associated with unusual ketosis or tendency to convulsions. Weymuller and Schloss¹⁸ found that a high fat diet produced a greater ketonuria in children subject to attacks of recurrent vomiting than in control children. They point out that no difficulty in storing glycogen exists (Levine and others²⁰). One is left then with two suppositions to explain attacks of ketosis in nondiabetic children: (1) Glycogenolysis may be unusually rapid during starvation, fever, high fat diet, or other disturbances. Under these circumstances certain patients apparently do not produce sufficient carbohydrate from the metabolic products of proteins to prevent ketosis. (2) Certain circumstances may lead to rapid burning of fat *per se* or a difficulty in storing circulating fat (Weymuller and Schloss¹⁸).

Since glycogen is stored chiefly in the liver and since the liver is the organ contributing the largest amount of ketone bodies to the blood,²¹ hepatic injury might be considered a likely lesion in pathologic ketosis. The frequency of enlarged livers in these patients may indicate hepatic lesions. However, diseases characterized by hepatic injury are not accompanied especially frequently by ketosis. Since the liver is apparently the chief site of formation of ketone bodies, any hepatic disturbance which explains nondiabetic ketosis probably does not affect this hepatic function. Furthermore, rapid burning of fat is accompanied by enlargement of and accumulation of fat in the liver. Autopsies in cases of recurrent vomiting are few^{22 23 24} and fail to reveal characteristic lesions of the liver, though fatty changes were noted. Although vomiting, ketosis, hypoglycemia, and hepatomegaly in von Gierke's disease suggest certain analogies to the ordinary cases of nondiabetic ketosis, the ready response of the latter to infusions of glucose, as well as the lack of reports of accumulations of glycogen in the liver at autopsy, make it unlikely that temporary, defective glycolysis analogous to that of von Gierke's disease occurs during attacks of nondiabetic ketosis. For these reasons no conclusions can be made as to the significance of the high incidence of enlargement of the liver in nondiabetic ketosis with acidosis. Hepatomegaly may indicate a functional or anatomic disturbance of the liver, or it may merely signify unusually rapid metabolism of fat.

For the present, one is probably on safe ground in assuming that *nondiabetic ketosis with acidosis is a potentiality in all children*. Little evidence exists that the recurrent or isolated attacks of ketosis with acidosis differ, except in degree, from what may be produced in normal children by starvation. However, one can scarcely doubt that some children, either because of their nervous make-up or a possible metabolic weakness, are more easily thrown into ketosis. Starvation due to vomiting is almost a constant contributing factor in cases with or without infections. Age is the most important predisposing cause since the frequency and severity of attacks of ketosis with acidosis is greatest in children younger than eighteen months. The specific effect of glucose orally or intravenously points to a deficit of available glucose as the probable immediate cause of nondiabetic ketosis. The deficit of carbohydrate may be due to exhaustion of reserves of glycogen or failure to metabolize sufficient proteins to supply glucose by glyconeogenesis.

SUMMARY

Serum electrolyte and clinical observations are reported on twenty cases of nondiabetic ketosis. Clinically, about one-third of the cases showed slight infections, one-third moderate infections, and the remainder, severe infections. Only three deaths occurred, and in two

of these septicemia was the apparent cause in the other fatal case no diagnosis could be made. In no case did acidosis per se lead to death. The type of infection did not seem to play a deciding rôle in the development of ketosis. The cases of severe acidosis occurred almost exclusively in infants aged less than eighteen months. Two cases with severe acidosis in newborn babies were described. Only three patients showed recurrent attacks of ketosis. Enlarged liver was almost a constant feature of the cases with marked acidosis. Recognition of the rôle of ketosis and acidosis in certain cases of severe infection leads to appropriate treatment and favorable outcome.

The reduction in bicarbonate was accounted for in some cases by accumulation of ketone bodies and in a few cases by increased concentration of chloride. Reduction in the concentration of total base (sodium) was not a prominent feature except in cases with severe infection. However since dehydration was a prominent feature of the cases with marked acidosis deficit of sodium and chloride was considerable. The blood sugar level was variable but did not show a consistent tendency to be unusually low.

Clinical experience, as well as the chemical findings in the blood indicate that treatment should be directed toward stopping the vomiting, restoration of the deficit of extracellular water and electrolyte and the administration of carbohydrate in order to insure conditions favorable to the combustion of glucose. Withholding food and water is frequently necessary on account of persistent nausea and vomiting. Intravenous infusions of glucose and hypodermoclyses of saline were apparently adequate for the restoration of the deficit of electrolyte and to combat acidosis. Administration of sodium bicarbonate by mouth led to considerable alkalosis in one case. This fact and the clinical course in other cases indicate that sodium bicarbonate is not necessary for the treatment of nondiabetic ketosis when sufficient physiologic saline or alkaline saline is given by hypodermoclyses.

CASE REPORTS

CASE 1—R. G. Recurrent vomiting, nondiabetic ketosis with acidosis.

The first admission (A) was Oct. 26, 1929, when the patient was fourteen months old. He had been ill for five days, starting with loss of appetite and repeated vomiting. Symptoms of acidosis developed the day before admission. The child was very sick, markedly dehydrated, showed Kussmaul breathing with the odor of acetone to the breath. The pharynx was red. The liver was palpated at the level of the umbilicus, 4 cm. below the costal margin. The patient received a hypodermoclysis of 400 c.c. of saline and an intravenous infusion of glucose about twelve hours before the first blood sample was withdrawn. After the blood was withdrawn, the child received three doses of 3 gm. of NaHCO_3 by mouth. Treatment consisted of hypodermoclyses of saline, infusions of glucose, and blood transfusions. The child vomited a few times until the third day in the hospital. Thereafter nourishment was taken, and recovery was uneventful. On October 10 the gastric juice showed Cl, 57; total base, 86; and titratable acidity, 13.6 milliequivalents per liter.

Note especially that the acidosis was accompanied by high chlorides and fairly high acetone. In spite of the hypodermoclysis on admission, the child weighed the same (10.1 kg) on the second day in the hospital. Adequate hypodermoclyses brought the weight up to 11.5 kg on October 30. Treatment with sodium bicarbonate and hypodermoclyses led to recovery from dehydration and a normal bicarbonate, but ketosis persisted until October 30. With the oxidation of the ketone bodies, alkalosis, which was apparently symptomless, developed.

The patient was readmitted November 16, after being home for ten days. The child vomited repeatedly for four days before the second admission (B). Prostration and dehydration were less marked than on the first admission. The liver was felt 3 cm below the costal margin. The boy was treated with 1,200 cc of saline subcutaneously, 60 cc of 20 per cent solution of glucose intravenously, and 2.5 gm. NaHCO_3 orally on the first day. Five units of insulin were given with the glucose. Twelve hours later the patient's weight had increased from 10.4 to 11.4 kg and he looked much better. On November 11, the gastric juice contained Cl, 30, and base, 13 miliequivalents per liter. The more rapid recovery during the second admission was attributed to the prompt administration of adequate amounts of saline rather than the insulin.

The family moved to New York, where the patient was followed in the Cornell Clinic. In the fall of 1933 he was seen by Dr. Vernon Lippard, who found that attacks of abdominal pain and vomiting associated with respiratory infections had occurred. These took place irregularly about every three months, no fever was noted by the parents, no air hunger developed, and admission to the hospital was not necessary.

CASE 2—S. R. (Colored) Recurrent vomiting, malnutrition, nondiabetic ketosis with acidosis

The patient was admitted to the hospital on Feb. 22, 1933, at the age of three and one-half years. In December, 1932, she suffered from moderately severe pertussis. Six days before admission she developed a cough and rhinorrhea. She vomited fourteen times on February 19 and showed ketosis when seen in the dispensary. Because she continued to vomit and failed to respond to treatment, she was sent into the hospital on February 22. On admission she was apathetic, undernourished, and showed Kussmaul breathing. The abdomen was scaphoid, and the liver was not palpated. Treatment consisted of hypodermoclysis of alkaline saline and infusions of glucose with insulin. Recovery was prompt with a gain in weight from 10.3 to 10.8 kg.

The patient was readmitted with a similar, but much milder, attack of vomiting and ketosis in September, 1933. No further attacks have occurred.

CASE 3—R. G. Recurrent vomiting, nondiabetic ketosis

The patient was admitted in July, 1928, at the age of three years, for an attack of vomiting which had lasted five days. He showed ketonuria and hyperpnea. No chemical studies were made. The patient thereafter was subject to a number of attacks of vomiting and ketosis which did not require hospital treatment. After vomiting for four days, he was readmitted Oct. 31, 1929, at the age of four years. Before admission the patient had been treated with orange juice to which NaCl had been added, but this was vomited. The face was flushed and the liver slightly enlarged. On admission analysis of the vomitus revealed Cl, 114, and total base, 67 miliequivalents per liter. He was treated with subcutaneous saline and intravenous glucose. Recovery was prompt. He was discharged November 4. There was no subsequent recurrence of attacks.

CASE 4—H. C. Nondiabetic ketosis with acidosis.

The patient was admitted Sept. 14, 1930, at the age of fourteen months. He had suffered a little more than the usual number of respiratory infections during the first year of life. Two weeks before admission he passed three or four foul, loose, green stools. The diarrhea continued until admission. He vomited three times during the eighteen hours preceding admission. Heavy breathing was noted the day before admission. The diarrhea may have been precipitated by eating green grapes. On admission he was well developed and nourished. The cheeks were flushed and Kussmaul breathing was present. Dehydration was only moderate. The abdomen was scaphoid, and the liver was felt 3 cm. below the costal margin. Treatment consisted of an infusion of 150 c.c. of 10 per cent glucose with four units of insulin. Improvement was slow but definite in twenty-four hours. No appreciable gain in weight occurred with recovery. It was felt that recovery was delayed by not using hypodermoclyses of saline.

CASE 5—R. R. Nondiabetic ketosis with acidosis congenital syphilis

The patient was admitted to the hospital when he was one month old because of failure to gain in weight. A positive Wassermann reaction and signs of syphilis were found. In spite of treatment the blood Wassermann reaction remained positive but the cerebrospinal fluid Wassermann reaction and colloidal gold curve were normal on fluid taken two days before present illness. The boy was admitted Aug. 3, 1934 at the age of five and one-half years. He had vomited repeatedly for the previous twenty-four hours. He was thin, moderately dehydrated, and looked fairly sick, the breathing was somewhat rapid and deep. The temperature was 38° C. on admission but normal thereafter. Subcutaneous injection of alkaline saline and intravenous infusions of glucose led to prompt recovery. He was discharged Aug. 9, 1934.

CASE 6—L. deR. Poisoning with methyl salicylate nondiabetic ketosis with acidosis.

The patient was admitted Aug. 24, 1932 at the age of two years. Three-quarters of an hour before admission the patient swallowed about 15 c.c. of oil of wintergreen. He vomited about one-half hour after being given milk. On admission a gastric lavage brought back a little mucoid material on which the odor of oil of wintergreen could be detected. The child did not appear ill. He was given an hypodermoclysis of 500 c.c. of saline and an infusion of 200 c.c. of 10 per cent glucose. Eighteen hours later he developed Kussmaul breathing, and the liver was palpated a little below the costal margin for the first time. Acetone as well as salicyl was detected in the urine. The temperature rose to 40° C. August 27, but was normal the next day. The patient was discharged well on Aug. 29, 1932.

The especial interest of this case lies in the development of ketosis within eighteen hours following ingestion of oil of wintergreen in spite of an infusion of glucose.

CASE 7—G. S., newborn infant. Congenital maldevelopment of the brain microcephalus nondiabetic ketosis with acidosis.

The patient was born at term and weighed 3,200 gm. She was covered with meconium, and difficulty in getting her to breathe was encountered. The baby nursed poorly from the breast and bottle for the first two days and probably got little food or water. Twitching of the mouth was noted on the second day. On the third day she was transferred to the pediatric service because of dehydration and deep breathing. She received 250 c.c. of saline before coming to the pediatric ward where the sample of blood was obtained. The patient was markedly dehydrated and very sick. The liver was not enlarged. Under treatment with intravenous glucose, subcutaneous saline, and transfusions of blood recovery was prompt. She was dis-

charged when fourteen days old. Subsequently at the age of six months, she was found to be spastic, lacking in higher cerebral functions, and microcephalic.

This patient illustrates that marked ketosis with acidosis may occur in a newborn infant.

CASE 8—A. L. Alimentary anemia, rhinopharyngitis, nondiabetic ketosis with acidosis.

The patient was admitted July 30, 1932, at the age of two years. He was a full term baby who was weaned at seven months but thereafter suffered an attack of diarrhea and was fed a diet consisting chiefly of milk and sugar. No cod liver oil or orange juice was given. At one year of age he appeared pale. He had five convulsions during the second year of life. On July 16, 1932, he developed fever, rhinorrhea, and vomiting but seemed better two days later. July 29 the boy had fever, cough, and a convulsion. Another convulsion occurred on the day he entered the hospital. On admission the temperature was 40° C. The child was fairly well developed but showed marked pallor, moderate undernutrition, and stupor. Breathing was of the Kussmaul type. The pharynx was red, and the voice hoarse. The spleen was palpated 4 cm, and the liver 6 cm, below the costal margin. The leucocyte count was 32,000, and the erythrocytes numbered 4.8 millions per cubic millimeter. The hemoglobin was 26 per cent (Sahli). The patient was treated with infusions of glucose and a hypodermoclysis of saline solution. Recovery from acidosis occurred in twenty-four hours. Recovery from the anemia occurred in about two weeks under treatment with iron and an adequate diet. He was discharged Aug 16, 1932.

CASE 9—R. P. Congenital malformation of heart, occult spina bifida, nondiabetic ketosis with acidosis.

The patient was known to have a congenital lesion of the heart since he was one year old. He had been subject to attacks of bronchitis. During the three months preceding the present illness, he had several attacks of blueness lasting several days. Jan 8, 1932, the patient developed cough and anorexia. Deep respirations were noted the day before admission. The patient was underdeveloped and poorly nourished. Respirations were rapid and deep, and an odor of acetone could be detected on the breath. Moderate cyanosis and clubbing of fingers was noted. The heart was enlarged, and a systolic murmur at the base was heard. The liver was felt 3 cm below the costal margin. The temperature was elevated (38° to 39° C) for a week. The ketosis disappeared within a day following intravenous infusion of glucose. A year later the boy died rather suddenly with probable heart failure. No necropsy was performed.

CASE 10—L. R. Upper respiratory infection, nondiabetic ketosis with acidosis.

The patient was admitted Mar 10, 1930, at the age of two and one-half years. He was taken ill rather suddenly with loss of appetite and vomiting on March 6. No vomiting occurred on the two days before admission to the hospital, but nothing was eaten on these days. On March 10 he became drowsy and on admission was moderately prostrated and showed Kussmaul breathing. The abdomen was scaphoid, and the liver was not palpated. Recovery from air hunger occurred in twenty-four hours following infusions of glucose and hypodermoclyses of saline. On the second and third days in the hospital the temperature was 39° and 40° C, respectively. No gain in weight occurred with recovery. He was discharged well on Mar 20, 1930.

CASE 11—D. B. Upper respiratory infection, nondiabetic ketosis.

The patient was admitted to the hospital Mar 18, 1930, at the age of four years. He had been ill for three days with fever, prostration, and repeated vomiting. On

admission he was fairly sick and showed deep breathing. The patient recovered promptly after two infusions of glucose and was discharged Mar 23 1930.

CASE 12.—J. W. Upper respiratory infection, nondiabetic ketosis.

The patient was admitted to the hospital on Apr 21, 1930 at the age of five years. She was taken ill April 17, with headache, malaise, and fever. The family physician thought the liver was enlarged at this time. From April 18 until admission, repeated vomiting occurred. On admission the girl was not very sick although she felt weak. The voice was hoarse, and the breathing deep. The patient was given a hypodermoclysis of 700 c.c. of saline, the first blood was taken eighteen hours later. Recovery was prompt. On April 23 a normal response was obtained to an intravenous sugar tolerance test. She was discharged Apr 29, 1930.

CASE 13.—H. O'B. Capillary bronchitis nondiabetic ketosis.

The patient, aged five years, was admitted to the hospital on Mar 15 1932. He was taken ill on March 13 with a persistent cough. Repeated vomiting and dyspnea developed the next day. On admission the patient was quite ill with fever (39.5 C) prostration, hoarseness, and deep breathing. Moderate retraction of interspaces was noted and diffuse, medium, moist rales were heard. The liver was not enlarged. No treatment was directed toward the ketosis. Recovery was rapid. Discharged March 28.

CASE 14.—M. W. (Colored.) Pneumonia (pneumococcus Type XXI), nondiabetic ketosis with acidosis.

The patient entered the hospital June 9 1934 at the age of two and one-half years. She had had a cold for one week and high fever for three days. She vomited three times the day before admission. On admission she looked fairly sick. The breathing was a little deeper than one would expect in pneumonia, and an odor of acetone could be detected on the breath. Signs of consolidation of the right middle lobe were found. The abdomen was normal. The liver did not seem large. The child's temperature remained elevated for three days in the hospital. On the second and third day in the hospital, the liver felt large (3 cm. below the costal margin) but the breathing no longer suggested acidosis. She was discharged June 20 1934.

CASE 15.—J. R. Scarlet fever mastoiditis dehydration nondiabetic ketosis with acidosis.

The boy entered the hospital on Apr 8, 1932, at the age of three and one-half years. He became ill with fever and malaise on March 31. The next day he vomited once but seemed to be recovering until April 5, when he vomited repeatedly. On the next two days the vomiting continued, and a rash appeared. On admission to the hospital the boy was well developed though he had evidently lost weight. He was markedly dehydrated and almost moribund. The respirations were of the Kussmaul type. There was marked pharyngitis, cervical adenitis, and otitis media. The abdomen was scaphoid, and the liver was felt 2 cm. below the costal margin. The blood for chemical examination was taken before treatment, and since the blood sugar was high, it was felt that the patient might be suffering from diabetes. He was treated with hypodermoclyses of saline and infusions of glucose with insulin. The recovery from acidosis and dehydration was fairly rapid (about forty-eight hours). Subsequently he developed desquamation suggesting scarlet fever. Mastoidectomy was performed April 23. Sugar tolerance was normal on April 16 and he was discharged well on April 30.

CASE 16.—R. Z. Scarlet fever septicemia (*Streptococcus hemolyticus*) multiple subcutaneous abscesses otitis media dehydration nondiabetic ketosis with acidosis.

The patient was admitted to the hospital March 4, 1930, at the age of three and one half years. On March 1 he developed fever, vomiting, and restlessness. A scarlatiniform rash appeared on March 2. Vomiting became frequent, and abdominal pain developed. On admission the boy was well developed and nourished, but acutely ill and greatly prostrated. Respirations were rapid and deep. The skin showed a typical scarlatiniform rash. The pharynx was red and swollen, the cervical lymph nodes, large and tender. The lower lip showed an ulcer with surrounding inflammation. The abdomen was not distended but was tender over the right upper quadrant. The liver was felt 5 cm. below the costal margin.

The boy continued extremely ill for four weeks and the temperature did not remain below 38° C until the sixth week. The boy seemed worse on the third day in the hospital. Blood cultures were positive for hemolytic streptococci for the first six days and twice thereafter, but they were negative after the tenth day. The breathing suggested acidosis for four days, and acetone was present in the urine for six days. Multiple subcutaneous abscesses developed.

The boy received scarlatiniform antitoxin, blood transfusions, and infusions of glucose the first day in the hospital. Thereafter he was treated with repeated transfusions of blood, infusions of glucose, and hypodermoclyses of saline. From the third to the seventh day he received insulin together with the infusions of glucose. Decrease in the size of the liver was coincident with disappearance of acetoneuria. He was discharged well on May 17, 1934.

CASE 17—F. P. Enterococcal septicemia, peritonitis, pneumonia, otitis media, nondiabetic ketosis with acidosis.

The patient, one year old, entered the hospital on Feb. 14, 1930. He had had a cold two weeks before but seemed to be getting better until February 10, when fever recurred. On February 12 the respirations were labored, on February 13 the stools became loose and frequent, and he vomited, on the day of entry into the hospital diarrhea and vomiting were frequent. On admission the patient was well developed, but extremely ill, prostrated, and markedly dehydrated. The abdomen was not distended, the liver was felt 2 cm. below the costal margin. The baby was treated with hypodermoclysis of saline, infusions of glucose, and blood transfusion. Signs of pneumonia and peritonitis developed before death on February 15. No autopsy was performed. Cultures of the blood and peritoneal fluid revealed *Micrococcus ovalis*.

CASE 18—E. L. Rhinopharyngitis, otitis media, bronchiolitis, bronchopneumonia, diarrhea, nondiabetic ketosis with acidosis.

The patient, aged one year, entered the hospital on Dec. 17, 1932. She became ill December 1 with cough, rhinorrhea, but no fever. She seemed to be recovering until December 5, when she vomited once. The next day she vomited after each feeding and passed twelve loose stools. The following day although she vomited but three times and passed but three loose stools, she looked much sicker and developed air hunger. On admission the temperature was 40°, and she showed marked Kussmaul breathing with an odor of acetone to the breath. Dehydration was very marked, sclerema being present. The abdomen was scaphoid, and the liver enlarged (2 cm. below the costal margin). The temperature remained 40° C for three days and then varied between 38° and 37.5° C for seven more days. The diarrhea continued for three days in the hospital. Although the serum bicarbonate became normal on December 9, the respiration remained rapid but suggestive of pneumonia rather than acidosis. Physical signs and a roentgenogram established the diagnosis of bronchiolitis and bronchopneumonia. Recovery from the infection was slow. She was discharged Jan. 12, 1933.

The baby was given nothing by mouth until the second day in the hospital when 10 per cent glucose was tried but was discontinued because of the vomiting. A mixture of skimmed milk plus dextrimaltose was started on the fifth day in the hospital. Hypodermoclysis of alkaline saline infusions of glucose and transfusions of blood were given during the first week. On admission 2 gm. of NaHCO_3 was given by mouth.

The patient has been followed in the dispensary through several infections without a recurrence of ketosis.

This patient probably suffered from an acidosis due to diarrhea as well as ketosis.

CASE 19—Boy B Newborn infant. Septicemia (*Streptococcus hemolyticus*) bronchopneumonia, encephalomyelitis nondiabetic ketosis.

The baby was born on Jan. 17, 1933 after a labor lasting nineteen hours and had to be resuscitated with artificial respiration and caffeine. The body was covered with meconium. Six hours later facial paralysis was noted. Twelve hours after birth he vomited material containing blood and the respirations were noted to be Kussmaul in type although periods of apnea occurred. Hypodermoclysis of 720 c.c. of saline was given during the first day. The extremities were spastic and tremors and strabismus were noted the second day of life. On the third day of life acetone was detected in the urine and on the breath. Fever (38.9 C) was present on January 19 and 20. The baby vomited repeatedly during the last three days of life. No note was made in regard to the liver.

Autopsy showed extensive necrobiosis, demyelination and glial proliferation of brain, confluent focal pneumonia, pulmonary congestion and hemorrhages. The liver was large (175 gm.) but showed only fatty infiltration histologically.

CASE 20—J. K. Nondiabetic ketosis with acidosis cause of death not determined anemia.

The patient entered the hospital on Oct. 4, 1930 at the age of eight months. Six weeks previously he had suffered for two days from a cold accompanied by vomiting. He was apparently well until October 1 when he vomited three times but seemed to have no fever or loss of appetite. He seemed better the next day though he vomited twice. The night before admission he vomited repeatedly and had two convulsions. On admission the temperature was 36.4 C and the respirations were rapid (40 per minute) and deep. He was well developed but dehydrated and comatose. The abdomen was scaphoid and the liver felt 3 cm. below the costal margin. The white blood count, 32,500; red blood count, 2.0 millions per cubic millimeter; hemoglobin 58 per cent (Sahli). The temperature rose to 38 C the next day and finally to 40 C before death on October 7. He was treated by hypodermoclyses of saline infusions of glucose and transfusion of blood. He never recovered from the coma although the signs of dehydration and acidosis disappeared. The spinal fluid was negative. No autopsy was performed.

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ALLERGIC REACTIONS TO SCHICK TESTS AFTER TOXOID IMMUNIZATION

REPORT OF TWO CASES

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ALTHOUGH untoward reactions to the parenteral injection of foreign protein into the human organism have been reported by numerous observers, a careful survey of the literature fails to reveal any reactions resulting from the injection of an intradermal test dose of diphtheria toxin as used in performing the Schick test. In the present communication, we are reporting two such instances.

CASE 1.—A twelve-month-old female infant with a past history of eczema was found on Oct. 24, 1932, to give a positive reaction to the Schick test. One week later she received subcutaneously 0.5 c.c. of diphtheria toxoid. Four weeks later she received a second injection of 1 c.c. of diphtheria toxoid. After four months the Schick test was repeated. Approximately fourteen hours following the intradermal injection of 0.1 c.c. of the standard dilution of diphtheria toxin, the child's skin became covered completely with urticaria. This persisted for hours. It was believed that an anaphylactic reaction resulted from the injection and that it was similar in mechanism to the reactions incident to a second injection of a foreign serum in a sensitized patient.

CASE 2.—An eleven-month-old female with a past history of eczema, was found to react positively to the Schick test on Nov. 15, 1932. Two weeks later she received 0.5 c.c. of toxoid. Three weeks later a second injection of 1 c.c. of toxoid was given subcutaneously and three weeks later an additional injection was given. After eight weeks, Mar. 7, 1933, a second Schick test was made on the child's right arm. The child was frightened at the time and cried before and after the procedure. Approximately two minutes later urticaria appeared on the child's face and soon extended over the body. At the site of the Schick test a large wheal developed. The infant's eyelids became swollen, and edema of the face was followed by laryngeal stridor and cyanosis. Four minims of adrenalin chloride (1:1000 dilution) were injected into the left arm while a tourniquet was applied tightly to the right arm above the elbow. In a few minutes the child appeared much relieved; the puffiness of the face subsided considerably, the cyanosis disappeared, the child breathed easily, and the urticaria rapidly faded. The tourniquet was released and within a minute all previous symptoms returned, including moderately severe cyanosis. The tourniquet was reapplied, and adrenalin in the same amount was again injected into the left arm. The symptoms rapidly subsided. When the tourniquet was released once more, it was immediately reapplied, released, and reapplied again. This procedure involved several minutes. It is believed the urticarial reaction, as in the previous case, constituted an anaphylactic reaction due to a second intradermal injection of foreign protein.

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DISCUSSION

The mechanism of reactions such as this is not entirely understood, but in light of the present knowledge of allergy it may be explained on the basis of a state of hypersensitiveness induced by previous injection of the specific protein. The possibility of repeated injection of toxin-antitoxin producing a state of hypersensitivity to horse serum in individuals has been discussed by several observers^{1,2,3,4,5}. However, since horse serum is not present in either toxoid or diphtheria toxin diluted for the Schick test, the reaction seen in the two cases mentioned certainly could not have been due to sensitization to horse serum. A plausible explanation, we believe, would be that a previous Schick test followed by toxoid injections sensitized these infants to the bacterial protein, the bacterial toxin, or the protein in the culture medium used in the production of the toxin.

A similar hypothesis was offered by Sugg, Richardson, and Neill⁶ in their communications. They report evidence that diphtheria toxin can function as an antigen in the production of anaphylaxis. In view of the facts that both children were eczematous and that in numerous other cases no such reactions have occurred, we may conclude not only that such reactions are rare, but also that they possibly may occur only in hypersensitive types of children.

In view of these two experiences it is felt that certain precautionary measures are indicated. First, such reactions, although extremely rare, probably should be borne in mind, and methods of combating them should be available. Such methods include the presence of adrenalin chloride and the knowledge that a tourniquet tied tightly enough to stop the pulse will prevent rapid dissemination of the injected material. This latter procedure, emphasized by Duke, may be of greater importance than the injection of adrenalin chloride. Waldbott⁷ refers to this procedure, which he found more efficacious than atropin or adrenalin chloride in combating reactions to injections. Another precaution offered is that in sensitive children the injections of toxoid be spaced more closely together than three- or four-week intervals. A third precaution would be to repeat the Schick test in sensitive children after six months, instead of six weeks, following the last injection of toxoid, thus avoiding a possible state of extreme hypersensitivity. Finally, in repeating the Schick test in children who are known to be allergic, it may be advisable to do a preliminary skin test with a dilution (perhaps 1:200) of the Schick material.

CONCLUSION

Hypersensitive individuals may become sensitized to the bacterial protein, toxin, or broth proteins in toxoid so that a Schick test made after toxoid injections may result in an anaphylactic reaction.

A tourniquet above the point of injection adds greatly to the relief of anaphylactic symptoms.

A skin test with diluted Schick toxin would appear to be indicated before a Schick test is made on an individual of the hypersensitive type who has received toxoid inoculations.

It is possible that emotional disturbances, particularly fright, may play some part in the precipitation of these anaphylactic reactions.

Such reactions, as reported here, are extremely rare and should not nullify proper preventive or prophylactic measures.

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Critical Review

INFECTION AND IMMUNITY PASSIVE IMMUNITY IN CONTAGIOUS DISEASES

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IN A previous article the fundamentals of immunity and infection were reviewed¹. This issue contains the report of a committee appointed by the Academy to consider the methods of active immunization employed in contagious diseases. A corollary to this report would be a commentative review on the methods of passive immunization.

Some general points about passive immunity should be stressed. Passive immunization is only temporarily beneficial, since it only tides the patient over a crisis caused by some specific element. It is usually specific for only one organism, either for its exotoxin, endotoxin, or bacterial fraction, it plays no part in repairing organs that have been previously damaged by the specific element, it is ordinarily found in the serum obtained from a human being or another species that either has had the disease or that has been actively immunized against the specific infection by artificial means.

Practically all serums used to immunize human beings passively are obtained from human beings or animals, i.e., the horse, sheep, or goat. Animal serums are prepared by commercial firms who must meet the strict requirements of the United States Public Health Service and are frequently checked by the government. This is not true of human serums, hence, one should investigate the source of any human blood plasma used in passive immunization. Such serums should be obtained from individuals who are negative reactors to the Wassermann test and who have no signs of tuberculosis or active disease of any kind. These serums should be inactivated at 56° C. for one hour before bottling, and a preservative should be added before storing. Some workers pass the material through a filter, add a preservative, and then store. All serums should be examined from time to time, and those that have become clouded or show signs of contamination should not be used. It is getting more difficult for the practicing physician to obtain convalescent human serums since most of the men who have the responsibility of preparing them hesitate to take the hazards of a chance infection that might result from any latent bacteria that might be present in serums that come from their laboratories. Although the average practitioner cannot carry out the procedure described in the foregoing, he can bleed a patient who is convalescing and allow the blood to flow into a citrated syringe. He can then inject the whole blood directly into the muscles of the patient to be passively immunized. One need not worry about blood

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matching when injections are made intramuscularly. Even with intramuscular injections, the plunger of the syringe should always be withdrawn after piercing the skin and when it is in situ to see whether there is any bleeding which would signify that a vessel had been entered. If the amount of blood to be injected at any one time is large, it should not all be delivered in one spot; this applies to commercial antitoxins as well. The injection of any material, even though it may be of a homologous source, is a foreign body and absorption must take place through an inflammatory reaction in which the white blood cells play a prominent part. If too much serum is injected into the muscles of one area, it is possible for a sterile abscess to develop which may have to be surgically evacuated. Neither should the injection of serum or antitoxin be made subcutaneously since there will be some delay in absorption; if this goes beyond seven or eight days following the injection a localized inflammatory reaction may occur and sloughing of the tissues follow, a sort of modified Arthus phenomenon. Serums and antitoxins should never be given subcutaneously, if for no other reason than to avoid the pain which follows such a method of injection.

When antitoxins are given, one should expect a certain percentage of the patients to have serum reactions. These are termed as immediate, accelerated, and late¹ (see Table I). The percentage of these reactions

TABLE I

Immediate Reactions

- (1) Fever with chills
- (2) pulmonary evidence;
- (3) generalized itching
- (4) generalized urticaria
- (5) nausea and emesis
- (6) any of the above associated with cyanosis, dyspnea, vomiting, convulsions, sneezing, gastrointestinal symptoms, unconsciousness, modified shock or arthritis.

Accelerated Reactions

The same types of reactions described above appearing within a few to forty eight hours after the injection of therapeutic serum

Late Reactions

Generalized urticaria alone or with arthritis, adenitis, gastrointestinal symptoms, and fever

depends upon the manner of administration and the type of antitoxin. There is a high rate of immediate reactions following the intravenous injection of antitoxins. In general, intramuscular injections are the safest from the standpoint of the practitioner. Homologous serums (convalescent serums) if injected intramuscularly give but few reactions other than fever and an occasional maculopapular sparsely distributed, but generalized rose red rash which comes on from seven to fourteen days after the injection.

The method of testing the value or efficacy of any passive immune principle either serum or antitoxin is by animal experimentation or by clinical experience. The number of diseases, the specific element of which may be conclusively tested by animal experimentation are few indeed. Thus it follows that clinical experience is the only way to judge the efficiency of a therapeutic procedure. With no measurable method of comparison differences of opinion are bound to arise as to the value of any particular method of passive immunization.

The clinical reasons usually given for employing passive immunization are that after its use the mortality rate is decreased, the patients feel better subjectively, the temperature drops, the pulse rate decreases, the period of convalescence is shortened, and the number of complications is fewer.

In our enthusiasm, however, we forget that often the patient dies from some cause other than the disease which started the process, that the employment of passive immunity may defeat the establishment of any permanent active immunity, that one epidemic of disease may be extraordinarily virulent and another mild in character, that every infection has its own natural history and that most acute diseases are self-limited anyway. It follows that it is difficult to evaluate the efficacy of a therapy used in such diseases. It is twice as difficult if the mortality rate is low and the disease is one which cannot be given to animals.

Measles —³⁻⁸Intravenous injections or transfusions of properly matched adult human blood (from 100 cc to 250 cc) or injections of convalescent measles serum as high as 50 cc intramuscularly are recommended for treating individuals ill with measles. The mention of any and all serums made from organisms (Ferry and Fisher, Tunnickoff, Caronia) or viruses (Degkwitz) that have been described as the specific causes of this infection is avoided, since such causative factors have not been accepted yet as proved etiologic agents. Transfusions or intramuscular injections of adult whole blood may be of some general benefit, but, since it has been recently shown that adult serum does not prevent susceptible children from contracting measles after exposure, it would appear that its therapeutic use would be equally doubtful. However, no harm is done and some general benefit may be gained from such a procedure. Even the efficiency of convalescent serum itself has been doubted. It is physically impossible to protect everyone, but it might be worth while to protect passively physical weaklings.

Mumps —From 10 cc to 40 cc of convalescent serum has been recommended to prevent orchitis. It is difficult to draw any conclusions since practically all patients recover from mumps and the complication rate is variable. The most one could say is that the injection of convalescent mumps serum is harmless.

Chickenpox —The injection of convalescent serum as a therapy for chickenpox would seem like a wasted effort since the complications of this disease are so few and the mortality rate negligible.

Whooping Cough —⁹⁻¹⁸Two procedures of treatment have been suggested, i.e., (1) whooping cough vaccine (Sauer) or endoantigens (Krueger) in the early stages of the disease and (2) convalescent whooping cough serum for the severely ill patient.

At first, one would be inclined to object to the injection of a specific element during the incubation period of an infection, since it might act in a synergistic manner and aggravate the disease. If one examines the reports in the literature and analyzes the personal experiences of men specializing along this line, it is clear that no matter what it accomplishes, it does not seem to aggravate the illness. One must likewise conclude that there is no conclusive evidence that such a therapy modifies the disease, although it might still be used on the basis that it might do some good, especially, since it does no harm.

Convalescent whooping cough serum has been recommended for the severely ill patient. Little is written on this specific point and it is difficult to draw conclusions. Recent work has tended to show that the antigen of the bacillus is not neutralized by convalescent serum but that the local reaction following the injection of a combination of an antigen and serum is actually accentuated. One would therefore be tempted to question the use of convalescent whooping cough serum. Nevertheless I have never heard of any accidents due to the use of such a serum. If I did use it, I would give it early in the course of the disease. It would seem worthless to give it late since the majority of deaths in whooping cough are caused by the effects produced by secondary invaders.

Scarlet Fever.—¹⁴ ¹⁵The reviewer previously analyzed the literature on the benefits of passive immunity in scarlet fever. The literature that has appeared subsequently has not caused him to alter his opinion.

In my experience, I have had all types of reactions—early thermic responses, thermic responses with urticaria and edema, late urticaria and an anaphylactoid phenomenon with three deaths due to, or hastened by, antitoxin. In most of our treated cases there was far more illness from the effects of serum sickness than from the scarlet fever. Is it worth while, then, to inject all our patients in the face of the mildness of the present type of scarlet fever, just to see them better a day or two sooner and have serum sickness, or would it be better to leave them alone and take our chances on the average course of the disease? I believe that all will agree that the ultimate fate of antitoxin therapy will be settled only in an epidemic with a high mortality rate. I myself have yet to see the data of a series treated with intramuscular injections of scarlet fever antitoxins which I could not without much discredit match with a series of my own untreated cases."

Personally I have a great deal of faith in human convalescent scarlet fever serum and use it in the same manner as other serums, i.e., from 50 c.c. to 100 c.c. intramuscularly, etc. If it is not available however, and in a severely toxic case I would certainly use antitoxin on the theory that it might do some good.

Diphtheria.—¹⁶ ¹⁷This is a disease for which we have a definite antitoxin, both preventive and curative if given early enough and in sufficient quantities, and yet the mortality rates average from 10 per cent to 15 per cent. To understand this, it must be remembered that the disease is an 'anesthetic type' of infection one that does not worry the parents until it is often too late. It likewise must be realized that this is an infection which produces its damaging effects only when its toxin gets into the blood stream and that any damage done to various organs before antitoxin is administered is repaired by nature only. All that antitoxin does is to destroy or to neutralize the free or uncombined toxin. There is likely to be more cardiac complications since the use of antitoxin than there were before its use became general because antitoxin now saves many individuals with damaged hearts who previously would have died with the infection.

Some general rules regarding passive immunization for diphtheria should be emphasized. Enough antitoxin should be given subcutaneously, intramuscularly, intraperitoneally or intravenously at the onset and in but one injection if possible. The reviewer has previously stated

that any antitoxin—and this includes diphtheria—should never be given subcutaneously, not only because of the pain that follows, but also because absorption is slow and a localized Arthus phenomenon may develop. Whether it should be given intravenously depends on the blood pressure. It is a waste of time to inject individuals with antitoxin either intraperitoneally or intramuscularly if the blood pressure is so low that there is not enough peripheral vascular circulation to absorb it. Antitoxin can be given intramuscularly to any patient with a good blood pressure, and it is less likely to cause reactions. Various amounts of antitoxin have been recommended in articles and texts—from 1,000 units to 5,000 units for infants and children and from 2,000 units to 300,000 units for adults. Twenty thousand units of concentrated antitoxin will be absorbed from the peritoneal cavity of a 250 mg guinea pig within twenty-four hours, therefore, one need not worry much about the use of too much antitoxin in infants. From a practical standpoint, it would seem better to forget about the age, sex, and weight, of a patient and give the mild and moderately ill patient 20,000 units intramuscularly and those who are severely ill and who have a lowered blood pressure 40,000 units intravenously. It may be that these doses will have to be increased, since from European sources has come information about recent epidemics of diphtheria caused by a more virulent form of the organism, the so-called diphtheria gravis. It is well to use massive doses of antitoxin in severe fulminating infections that appear to run counter to our average experience. It has been shown that the toxin of the gravis organism is more virulent than that produced by the ordinary Park No 8 bacillus. The latter is used to make antitoxin in this country. Park No 8 antitoxin can neutralize diphtheria gravis bacillus if enough is given. In cases that appear to be malignant, large doses of antitoxin, as high as 100,000 units or more, are indicated.

Epidemic Meningitis—²⁴ ²⁵Antimeningococcus serum is used for passive immunity. This is not an antitoxin, but a serum with bacteriostatic or bacteriocidal qualities. Recently a soluble toxin of meningococcus was described, and some effort is now being made to produce a serum that is both bacteriocidal and antitoxic. This may be of some value since the mortality with this infection is high in spite of the use of specific serums. Innumerable articles have been written about the therapeutic results obtained with the use of antimeningococcus serum, and from these it is apparent that the fulminating toxic type of disease is usually not very amenable to any treatment and the patients die within from six to forty-eight hours. Often the diagnosis is not even suspected until some other patient begins to show the usual picture of a relatively more chronic type of meningitis (relative in the sense being a matter of a few days). Ignoring the infant and toxic fulminating types, the mortality rate may be as low as 15 per cent in certain series of cases treated with antitoxin.

If there is going to be any improvement, it should occur promptly. Since this disease is notorious for its relapses, it is advisable to taper off the treatment over a number of days in order to avoid the possibility of shock in case there is a relapse and serum has to be given again (usually from seven to fourteen days after the last treatment). One should be careful not to mistake the meningeal serum sickness re-

action, occurring from about seven to fourteen days after treatment ends, as an exacerbation of the disease since further specific treatment in these cases would aggravate the condition.

Smallpox—There is no need for any therapeutic serum since active immunization properly applied is 100 per cent protective

Poliomyelitis—^{25, 27, 28}The serum has yet to be described that will prevent the disease from developing in the monkey injected with the virus although some serums have prolonged its life a few days. Theoretically in the human being, convalescent poliomyelitis serum should be given in the preparalytic stage but usually the diagnosis is not made until there is frank paralysis. Whether convalescent poliomyelitis serum will stop the spread of paralysis is questionable. Recent surveys were not conclusive as to its value, but since it does no harm and might do some good, there is no definite contraindication to its use. From 10 to 20 c c of serum may be given intramuscularly, although recent articles indicate that larger doses would be more effective.

Erysipelas—²²⁻²⁷Erysipelas is one disease the natural history of which ought to be studied before conclusions are drawn about the beneficial effects of therapeutic antitoxins. Most of the articles written about the results obtained after the use of erysipelas antitoxin may be variously interpreted.

The personal opinion of the reviewer is that the antitoxin is not of much value save in the treatment of infants. There is however this comforting thought that the patients with erysipelas tolerate the injection of this antitoxin well and relatively few of them have serum sickness. It does not seem to harm the individual and it might do some good.

Encephalitis—A principle of passive immunity has not been developed for this disease as yet

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American Academy of Pediatrics

FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CLEVELAND, JUNE 11, 1934

Round Table Conference on the Newborn

Leader Dr Arthur H Parmelee, Oak Park, Ill Assistant Dr H N Sanford Chicago Ill

CHAIRMAN PARMELEE—This morning a round table discussion is to be on the subject of the newborn, with special emphasis on respiratory and circulatory disturbances.

We are all interested in increasing our knowledge of the newborn for the purpose of applying that knowledge in lowering the mortality of the hazardous period of transition from intrauterine to extrauterine life.

The newborn infant must rapidly adjust himself to many profound anatomic and physiologic changes. This adjustment complicated and difficult as it must be under the most favorable conditions becomes all the more difficult because of the traumatic insults of the birth process from which no infant can entirely escape.

The ability of the infant to make these physiologic and anatomic adjustments will depend largely upon three factors (1) the inherent vitality (2) the degree of maturity at the time of birth and (3) the extent to which pathologic conditions disturb the normal course of events.

The problems of respiration and circulation in these infants are two closely related functions and can hardly be dealt with separately. Difficulties encountered by the newborn in adjusting himself to his new mechanism of gaseous exchange will affect and in turn be affected by, the adjustments going on in the circulatory system.

The physiologists, embryologists and anatomists have busied themselves with these problems and have in some instances taken us to task for our ignorance. Many clinicians have also made valuable contributions to our knowledge of these vital phases of the newborn infant's adjustment. I shall attempt to outline briefly some of the features which seem to me of practical importance, but, as I do so I should like to have you keep in mind that in our clinical work we are dealing with individual infants. The ability of each individual infant to make his adjustments depends not only upon what may be proved to be a normal physiologic response to certain stimuli, but as well upon the three factors mentioned above, i.e., the inherent vitality (constitution) the degree of maturity and the pathologic conditions that may be present to disturb the normal course of events.

The Initiation of Respiration—Respiratory activity begins under normal conditions, almost simultaneously with the birth of the infant. That the initiation of

respiration is due to stimulation of the respiratory center and that CO_2 is the chief stimulant material is generally conceded. But the factors which govern the action of the stimulus are numerous, and the explanation of disturbances of respiration is a complicated one.

Schmidt says that the chief element in the chemical regulation of respiration is the concentration of the stimulant material within the cells of the respiratory center. Thus, he says, is dependent upon a balance among three factors: the concentration of the stimulant material in the arterial blood, the rate at which stimulant material is produced within the cells of the center, and the rate of blood flow through the center, which rate determines the extent to which stimulant material can accumulate there. That the respiratory center is influenced directly by changes in its blood supply and that respiratory response to changes in systemic blood pressure depends chiefly upon changes in cerebral blood flow have been experimentally proved. Normally an increase in cerebral blood flow depresses respiration, and a decrease stimulates respiration. This suggests that products of metabolism of the cells of the center play a part in regulating the activity of the center. But there is an abnormal condition of the center in which respiration is depressed by a decrease in its blood supply and stimulated by an increase. This abnormal relation is designated the "reversal."

Apparently the ability of the respiratory center to respond to stimuli depends upon a supply of oxygen adequate to support the metabolic processes upon which the functional activity of the cells depends. The reversal cannot be produced by an excess of CO_2 in the blood as long as the blood oxygen content is not markedly reduced and the cerebral circulation is adequately maintained, but it is readily produced by a general anoxemia or by a reduction of the cerebral blood flow. Schmidt says that any agent normally a stimulant to respiration may cause depression or failure if applied in the presence of oxygen deficiency in the brain consequent to subnormal cerebral blood flow.

These observations led Krafka to the conclusion that the apnea of intrauterine life is due to the phenomenon of reversal produced by a physiologic anemia. He suggested also that occlusion of the umbilical arteries by increasing the peripheral resistance raises the systemic blood pressure and increases the cerebral blood flow. This relieves the apnea, the high carbon dioxide concentration prevailing acts as a respiratory stimulus, and respiration is initiated.

In an excellent summary of his experimental work Schmidt makes the following statements: "The chief function of the entire respiratory mechanism is the maintenance within the center of a constant concentration of stimulant material. Factors known to be concerned in this maintenance are: changes in arterial blood, through changes in pulmonary ventilation, acid excretion by the kidneys, etc.; changes in the metabolic activity of the center, possibly concerned in the irritability of the center and in the reflex regulation of breathing; changes in the blood supply of the center, through local vascular and general vasomotor responses, which influence removal of metabolites from the center. Respiratory activity at any instant depends upon a delicate equilibrium among these factors and can be altered by changing any one of them."

Continuing, he says, "The nature of the stimulant material responsible for the regulation of respiration cannot be determined until more definite information is available concerning the part played by changes in the vessels supplying the center. The material is derived from the metabolism of cells, including those of the center, and it is probable that CO_2 is more important to the normal regulation than oxygen lack because the latter tends to modify the activity of the center by producing the reversal."

Asphyxia of the Newborn.—According to Seltz, 3.5 per cent of all infants are born in a condition of deep asphyxia. While some cases of asphyxia are due to local obstruction to the air passages, the majority result from a depression of the respiratory center.

The factors involved in this state of depression have been discussed. In the premature infant we have the additional factor of immaturity of the respiratory center. The significant part played by intracranial injury in the etiology of severe asphyxia is well recognized, and the remarks already made concerning the factors regulating respiration help to make this understandable.

In premature infants asphyxia at birth is, according to Yllpö, no more frequent than in full term infants. Its etiology is the same as for full term infants plus the factor of immaturity of the central nervous system. A peculiar type of breathing called periodic breathing is said to be physiologic for premature infants. It has been produced experimentally by primary changes in the blood supply of the center. The unstable vasomotor mechanism of the premature infant is probably an important factor in the occurrence of this phenomenon. Riihå and Salami, pupils of Yllpö, have expounded the theory that the high hemoglobin content of the blood in the newborn and especially in the premature may play a part by binding more oxygen and thus reducing the amount of stimulant material in the blood. Oxyhemoglobin is a stronger acid than is reduced hemoglobin, and the more oxyhemoglobin in the blood the less CO is it able to bind.

In the premature infant we have also an asphyxial state which develops in the second or third week of life, or even later. The explanation of this condition is not yet satisfactory. According to Ekstein, the autopsy findings are inconstant and not characteristic, sometimes including cerebral hemorrhage and only some and then atelectasis of any degree.

A functional inferiority of the central nervous system which does not produce symptoms until a certain stage of development is reached, suggests itself. However there are probably many other factors. The weakness and eventual fatigue of the muscles of respiration may play a rôle.

Atelectasis.—In medical literature and in medical parlance generally there is much loose talk about atelectasis. A rather thorough consideration of this subject, so that we may have some degree of uniformity in our conception of atelectasis, would seem to be very much in order. I believe we are well agreed that the lungs of the normal full term infant undergo gradual inflation during the first few days of life and that during this time a variable amount of initial atelectasis is present in all normal newborn infants.

This, if our belief is a fact, can rightfully be called 'physiologic atelectasis of the newborn. Physiologic peculiarities of the newborn sometimes take on pathologic proportions. This is true in regard to atelectasis. Various hindrances to the respiration of the newborn may result in the persistence of atelectasis to a pathologic extent. The persistence of large areas of atelectasis may be an important factor in causing death. However more important for us is a knowledge of the factor or factors that cause the atelectasis.

Besides this primary type of atelectasis, there are secondary types—resorptioo atelectasis for example, in which areas of lung that have been inflated become obstructed due to some hindrance to normal respiration and the alveoli collapse as the air is resorbed from them. Yllpö among others believes that primary atelectasis even in the premature infant is comparatively rare and that a secondary type is much more common. In the premature infant he maintains that nearly all of the small alveoli are inflated within a few hours after birth but that they soon become filled with blood constituents through exudation resulting from passive congestion.

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1900 showing that mixing of superior and inferior caval blood occurs in the right atrium. We might not know but we are glad to learn that Kellogg verified Pohlman's experiments in 1928.

I wish to call your attention to Patten's work which, if true will give us a new attitude toward the circulation in the fetus and in the newborn. He has shown that the apparent capacity of the foramen ovale of the fetal heart is greatly reduced by the manner in which the valvula is attached to the septum and that the effective interatrial passage in the heart of the full term fetus is a scant half of the size of the foramen ovale and little more than 40 per cent of the size of the inferior caval orifice. Because of its small size the foramen ovale cannot pass on to the left side enough blood to equalize intake on the left with intake on the right. In view of the fairly equal development of the two sides of the fetal heart, any assumption that they do not handle approximately equal amounts of blood is untenable.

The neglected factor in the situation is the pulmonary circulation. All the implications are against the current view that the pulmonary circulation is negligible. The actual size of the pulmonary veins indicates that they bring into the left atrium a volume of blood somewhat greater than that contributed by way of the restricted functional orifice of the foramen ovale. These facts make it necessary to change our previous theory of an abrupt increase in the pulmonary circulation at the moment of birth. He measured the size of the pulmonary arteries, the umbilical arteries, the pulmonary veins, and umbilical veins and concludes that, if the pulmonary vessels are carrying a circulation in any way consonant with their size, there is enough blood already going to the lungs before birth to care for oxygenation as soon as the lungs are inflated. In regard to the postnatal changes in circulation, he discredits the idea that there is any marked or abrupt change in the relative pressure in the two sides of the heart when placental circulation is interrupted. He says "As far as the heart is concerned the immediate result of tying off the umbilical vessels is merely to eliminate from the fetal circulation the blood that happened to be passing through the placenta at that moment. It can have no more effect on relative pressure in the two atria than loss of the same amount of blood by superficial hemorrhage."

The establishment of an adult type of circulation is accomplished gradually. All the primary readjustments appear to be fairly well accomplished by the end of the first month or six weeks. The final steps are then taken in a leisurely fashion.

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DR. HEYWORTH N. SANFORD (Chicago)—Dr. Parmelee has outlined the mechanism whereby the respiratory stimulation necessary to establish normal respiration at birth is begun. Asphyxia neonatorum is, therefore a failure for some reason of this normal stimulation to begin naturally.

The etiology of asphyxia neonatorum has been classified by McElroy as follows

I Intranatal causes

A Suffocative

- 1 Compression of the uterus
- 2 Interference with the umbilical circulation
- 3 Interference with the placental circulation as in such diseases as toxemias from syphilis, chronic infections as nephritis, and heart disease, and acute bacterial infections All these reduce the normal blood supply by placental infarcts
- 4 Prematurity, by predisposing to prolapse of the cord, and head injuries, and by faulty development of the respiratory mechanism
- 5 Drugs anesthetics, such as morphine, pituitrin, and ergot

B Paralytic

Cerebral hemorrhage from forceps, breech presentations, and long labors

II Postnatal asphyxia

A Injury to the head or cord by delivery methods

B Forcible methods of resuscitation that aggravate preexisting conditions

The symptoms are usually stated in obstetric textbooks as falling into two main groups Roughly, asphyxia livida is almost always due to the suffocative type and is the result of the aspiration of mucus, amniotic fluid, blood, or meconium The infant is cyanotic, although the lips are pale The general muscle tone is rigid, and there is a rapid response to stimulation. The second type, asphyxia pallida, is almost always due to the paralytic type of etiology With this the child is white and flaccid, and there is little or no response to stimulation.

In the actual diagnosis it is not possible in the presence of immediate asphyxia to go into much detail. Roughly, we have asphyxia if cyanosis is persistent, intermittent, or tardy A weak or grunting cry with shallow respiration usually indicates a cerebral hemorrhage Occasionally with intensive atelectasis the percussion note is dull, the breath sounds are decreased, and râles are heard over the atelectatic area Unfortunately these are not found in every instance—enough to make a positive diagnosis Dunham has drawn attention to the x ray as a means of differentiating atelectasis from other forms of lung pathology, such as pneumonia, pneumothorax, thymic enlargement, cysts, emphysema, and diaphragmatic hernia.

In the treatment I have thought it best to take up in detail the various measures in vogue, with the arguments for and against their use

1 *Body Manipulations*.—Such procedures as the Schultz maneuver and the like have long been in vogue by obstetricians and are still to be found in practically all obstetric textbooks These vary from massaging the skin and slapping the child to vigorous swinging in the air These methods are more notable for their spectacular violence than the results obtained, and they are now generally condemned They undoubtedly account for the unnecessary death of many babies each year

In the presence of intracranial injuries such procedures are even more dangerous Crothers has pointed out that even rhythmic compression of the chest, which cannot possibly favor the entrance of air into the collapsed lungs, serves only to pump blood into an already damaged head and brain. The condemnation of all such methods is to be praised.

2 *Temperature Stimulation*.—The use of hot and cold water for stimulation of the skin is also a common practice Cold water only serves to lower the general body temperature, and thus the general resistance of the child We find that the majority

of newborn infants come from the delivery rooms with subnormal temperatures even under the best of conditions. Cold water as a stimulant is unphysiologic and should be as much condemned as body manipulation.

Immersion in warm water, on the other hand, while of no value from a stimulation sense, does preserve the child's body temperature, and hence, its resistance. It simulates intrauterine life and is helpful to the child's well being.

3. Removal of Foreign Material—This is one of the most important procedures of resuscitation. It must be remembered that before satisfactory respiration can occur, the air passages must be cleared. The aspiration of amniotic fluid, vernix caseosa, lanugo hairs, and epithelial cells furnish one of the most common causes of pneumonia. Farber and Sweet found amniotic sac contents in the lungs of 88 per cent of 124 infants. The obvious necessity of removing foreign material from the air passages before any type of stimulation is attempted needs special emphasis.

This, again, should be accomplished by simple means. A common soft nosed rubber catheter, size 12, can be used with safety in the mouth and nose. After birth the baby can be laid for a moment with the head lower than the body and the larynx, and trachea milked toward the mouth. The catheter is then resorted to, to clear out the nose, mouth and throat.

Especial emphasis should be laid on the use of soft catheters and not too vigorous manipulation, as damage may be done to the nose and soft palate. The practice of wiping out the infant's mouth with a piece of gauze is to be condemned as it only serves to injure the delicate mucous lining.

4. Resuscitation With Air or Its Constituents.—*a. Air* This is one of the oldest means of combating asphyxia neonatorum and is particularly important because of its ease of administration. In its simplest form this consists of breathing into the mouth of the newborn infant. The use of other respiratory gases in the last few years has rather decreased the use of this simple method, also there are two drawbacks to its use.

The first is the contamination of the mucosa of the air passages of the newborn with the breath of the resuscitator particularly if he is suffering from a cold or is a carrier of bacteria. The second is the danger of rupture of the alveoli by too much air pressure. As to the first criticism, the practice of direct mouth-to-mouth breathing is certainly bad. This can be avoided, however, by placing several thick pieces of gauze between the mouth and nose of the newborn and the resuscitator or by the use of a tracheal insufflator equipped with a stop bulb.

The problem of too much insufflation may be overemphasized. Since Standler, Davis and Stevens observed 1 per cent of spontaneous pneumothorax in 702 routine x-ray examinations of newborns, this may be more common than is ordinarily supposed. However I have never seen a case of lung damage from mouth-to-mouth insufflation. There is no doubt that care should be used, and this applies to intra-tracheal insufflation as well. From 15 to 20 c.c. of air under a pressure of 15 to 20 mm. of mercury is sufficient to inflate the lungs of the newborn. Thus very little exhalation is needed to accomplish the desired pressure.

b. Oxygen This has long been the standard treatment, and there is no argument against it. It is now so commonly used in combinations with carbon dioxide that they will be considered together.

c. Carbon Dioxide Henderson, acting upon the knowledge that in the adult a partially asphyxiated respiratory center requires more carbon dioxide to stimulate it, advocated the administration of carbon dioxide to stimulate respiration in asphyxia neonatorum. McConnell and McCormac reported that in the use of oxygen alone for three years, there was no decrease in the mortality of asphyxia neonatorum but that in using 5 to 25 per cent carbon dioxide in combination with oxygen, they found the mortality was greatly lessened.

At first, expensive inhalators were devised to dispense the carbon dioxide and oxygen in the correct proportions, but these are not essential, for tanks of the mixed gases may be purchased from any medical supply house. Two different proportions can be obtained, one with 5 per cent carbon dioxide and 95 per cent oxygen, and the other with 10 per cent carbon dioxide and 90 per cent oxygen.

The amount of carbon dioxide given varies from 5 per cent to 30 per cent. Henderson advocates 7 per cent. Boothby says that higher mixtures are dangerous. Those who use higher mixtures say that if the mixtures cause gasping or struggling, they should be stopped, not abruptly, but by gradual lowering. Nearly everyone advocates giving the mixtures at not longer than five to ten minute intervals several times a day.

While the efficacy of carbon dioxide stimulation is generally accepted, there are some dissenting ideas that have never been satisfactorily explained. Eastman has found that the carbon dioxide tension of the fetal blood is normally higher than that of the maternal arm vein. One must assume, therefore, that in utero the sensitivity of the fetal respiratory center is depressed by carbon dioxide. Furthermore, the primary blood change in asphyxia neonatorum is a reduction of the oxygen content of the blood to extremely low levels. The serum pH of an asphyxiated infant is reduced to unsupportable levels, sometimes below 7.00. This indicates that the use of carbon dioxide as a resuscitating agent in asphyxia neonatorum is not only superfluous, but may even be harmful. What the infant needs is oxygen or air.

I simply wish to show that perhaps it is the oxygen in the mixture that is the cause of the good results. Coryllos has shown that oxygen passes more easily from the air sacs to the blood when carbon dioxide is present. This may be another reason. Until these questions are settled, it would be wise to continue the use of 5 per cent carbon dioxide and 95 per cent oxygen mixture, but certainly not in a greater proportion. Personally, I have never observed any different effects from the added carbon dioxide than were observed with pure oxygen.

There is one exception to this—in infants suffering from morphine narcotization. Here the respiratory center is apparently depressed far below its normal function. Shute and Davis in 120 narcotized infants used carbon dioxide in 10 to 30 per cent mixtures with oxygen in thirty-six of these infants and had but two deaths, while of the eighty-four who were not so treated, eight died.

d. Drinker Respirator. Murphy and Sessions used this apparatus in 1922 with great success, and it has been used much since. They state that there were no injurious effects and that it was of value in all types of asphyxia neonatorum, particularly in premature infants. We have been using the Drinker respirator routinely for the past five years. We believe that it can be used in all types of asphyxia neonatorum except those due to cerebral hemorrhage. The reason for this is that in the respirator the head is lower than the body, and, until the infant accommodates himself to breathing, there is considerable crying and struggling. I think that all this must only aggravate the hemorrhage, and in any case the trouble is cerebral and not in lung aeration. Second, before respiration begins, any material occluding the upper air passages must be cleared out, as has before been stated. You cannot aerate the lungs until the air passages are clear, and there is a possibility of drawing the material down into the bronchi and air sacs.

Practically, we use only a negative pressure of 10 mm. of mercury. Murphy advocated a positive pressure as well in severe asphyxia, but we have never used it. The respirations are set for thirty per minute, and the child is never kept in the respirator for more than one hour at a time. Several hour treatments may be given during the day. In premature infants with recurrent cyanotic attacks, treatments may be given for several days. I have given them for as long as two weeks. There is some idea that the respirator may injure the child.

Murphy and Bauer, in thirty antopeles on infants who died after respiration, found that there was a slight increase in pulmonary congestion but that no cellular material was found in the air passages. They concluded that there was no evidence of injury and that in atelectatic conditions the pressure could be increased to 15 mm. of mercury.

The respirator has also been criticized because it fails to regulate the carbon dioxide content of the circulating blood. To me the clinical success of this method answers the criticism and further raises the argument as to the necessity of carbon dioxide.

I do not believe that any method has been satisfactorily devised to treat severe atelectasis, but the principle of the respirator is as good as any. It offers an instantaneous method for creating a satisfactory degree of pulmonary ventilation accurately.

The chief drawback to the Drinker respirator is its costliness and this is a serious one. I do not think the respirator is particularly necessary outside of its ease in handling the infant. Certainly no one should feel that any particular infant who could not have been saved by other methods could have been saved by a respirator.

c. *Medical Stimulants*. Naturally all manner of cardiac and respiratory stimulants have been used have had their vogue, and later have been discarded. Among these are digitalis preparations, adrenalin, and more recently lobelin. The first two are of doubtful value. Certainly in cerebral hemorrhage, they might be harmful by increasing the blood pressure and causing more hemorrhage. Lobelin is presumed to be a direct central respiratory stimulant. Its administration intramuscularly or by injection into the umbilical vein is a simple way to try and stimulate respiration. The drug is safe, except in large doses or in too frequent doses. Lee reports two deaths in infants from its use.

Bonar has summed up certain principles that should be applied as universal in the treatment of asphyxia neonatorum.

1. All measures of a violent nature should be prohibited.
2. Absolute rest, warmth and quiet should be maintained.
3. The air passages should be cleared immediately.
4. Adequate fluid intake should be maintained.
5. Oxygen, or regulated doses of 5 per cent carbon dioxide and 95 per cent oxygen, should be administered.
6. In the absence of gases extremely gentle intratracheal insufflation of air, or possibly mouth-to-mouth insufflation should be used.
7. The administration of lobelin in moderate doses should be tried.
8. Asphyxia, complicated by evidence of intracranial pressure, seems to justify immediate treatment, either by giving blood injections, removal of an adequate amount of cerebrospinal fluid, or both.
9. Recurring attacks of asphyxia should receive the same attention as immediate asphyxia.
10. Roentgenograms of the chest are of great value in determining the cause of the cyanosis.

DISCUSSION

CHAIRMAN PARMELEE.—You have heard Dr. Sanford's thorough discussion of the respiratory difficulties of the newborn with special reference to treatment. I should like to have all of you enter freely into the discussion of this important subject. If Seitz's statement that 3.5 per cent of all infants are born in a state of deep asphyxia is true, the subject is indeed important.

DR. R. N. ANDREWS (MANKATO, MINN.) asked whether the use of a tracheal catheter in resuscitation was considered dangerous. He reported the case of an

infant thus resuscitated who died after thirty six hours, necropsy showed ruptured alveoli in addition to bronchopneumonia

He also inquired about the value of dilating the anal sphincter as a means of stimulating respiratory activity

DR P A McLENDON (WASHINGTON, D C) described an apparatus used in Washington for resuscitation called the Christman apparatus, with which very good results have been obtained.

He spoke also of the danger of cramped position of the infant's head in interfering seriously with breathing. He advocated placing some sort of a pad under the shoulders of an infant having any respiratory difficulty and leaving the pad there until he is breathing normally

DR C E BRADLEY (TULSA, OKLA.) made a plea for better teamwork between obstetricians and pediatricians in the technique of resuscitation. He felt that the practice of tilting the bassinet so that the infant lies with his head lowered for the first hours of life is not physiologically sound and is more likely to do harm than good.

The frequency of intracranial injury as a cause of respiratory difficulties would seem an important reason for restricting manipulations to the minimum

DR I R COHN (TOLEDO, OHIO) spoke of the possible rôle of sepsis in the etiology of atelectasis. He asked how infants with secondary atelectasis can be aided in the inflation of their lungs without the aid of a respirator

DR GEORGE R MURPHY (ELMIRA, N Y) emphasized the importance of first clearing the air passages before using any type of respirator or resorting to other manipulations. He spoke favorably of the Flagg resuscitation apparatus. The urgent necessity of teamwork in obstetrical and pediatric departments was stressed.

DR E R McCLUSKY (PITTSBURGH, PA) spoke of his experience with a European respirator, a modification of the Drinker, but operated on the same principle. He spoke of his experience with an oxygen tent which is a modification of the Cecil Blummer tent made to fit over a crib or a bed for a premature infant. In this, oxygen is kept at a concentration of about 50 per cent and set at that so it cannot be changed. One great advantage of this method is that the child can be put in it and left there for some time. Oxygen alone instead of a mixture of carbon dioxide and oxygen is being used more and more. It was his impression that they were getting better results with the oxygen tent method than with the respirator.

DR JAMES KRAMER (AKRON, OHIO) spoke of attacks of asphyxia occurring in the first days of life in babies with a cleft palate deformity, the tongue causing complete obstruction of the nasopharynx. He also referred to infants having attacks of coughing and cyanosis each time they were fed, seven cases of this sort had come under his observation, and all seven infants had finally died of bronchopneumonia, one of these infants lived a year.

DR THURMAN B GIVAN (BROOKLYN, N Y) described an inexpensive and satisfactory apparatus for administering oxygen to newborn infants.

DR S C HENN (CHICAGO, ILL) said that while it was important to keep infants with asphyxia from being chilled, it was wise to avoid overheating such as might occur in certain types of incubators. He spoke of the aid in diagnosis of the cause of respiratory difficulty that might be obtained from roentgenograms.

DR DAVID J LEVY (DETROIT, MICH) spoke of cyanotic attacks occurring in the first days of life in infants having loud systolic cardiac murmurs which dis

appeared within a week or so. Roentgenograms taken during the period of cyanosis and dyspnea showed great enlargement of the heart, and films taken after ten days showed a heart of normal size.

DR. A. LEVINSON (CHICAGO ILL.) thought there was danger of confusion in our discussion when we spoke one moment of asphyxia, then of cyanosis, and then of atelectasis, while apparently talking about the same thing. He spoke of the difficulties encountered in making a clinical diagnosis of atelectasis even with the aid of roentgenograms.

Intermittent cyanosis he felt was usually due to intracranial hemorrhage, while continuous cyanosis is usually due to a heart condition. These two conditions are not always easily differentiated. In either case the child should be kept strictly quiet, not taken to breast, not bathed, not weighed or handled at all. The child is fed by a dropper and given oxygen.

The infant just born and in a state of asphyxia needs to be treated. He agreed with Dr. Sanford's methods of handling these cases but had not used the Drinker respirator because of fear of the damage it might do to the lungs.

Oxygen alone he felt was preferable to mixtures of oxygen and carbon dioxide, and he considered oxygen a very valuable aid in treatment.

DR. H. GORDON (BROOKLYN N. Y.) advised caution in making a diagnosis of enlarged thymus as a cause of respiratory difficulty. Cyanosis is sometimes due to more obscure changes occurring in the process of transition from prenatal to postnatal conditions. Before birth the adrenal cortex is very large and has a good deal to do with tissue respiration. Upon the beginning of pulmonary respiration, there is immediately a change, the child must adapt himself to the new environment with the increase in oxygen tension and also in oxygen supply. As a result in some instances infants show weakness and inability to adapt themselves. In such cases we find a good deal of cyanosis.

He also spoke of the danger of damage to the lung tissue in the use of the respirator.

DR. SANFORD said that in five years of use of the respirator no child at necropsy had showed any damage to the lungs. This may be because infants are never kept in longer than an hour at a time, no positive pressure apparatus is used, and negative pressure is never more than 10 mm. of water.

DR. S. H. ASHMAN (DAYTON OHIO) cited the case of an infant born normally who at birth was cyanotic, had physical findings of atelectasis, and had also an asthmatic type of breathing. A roentgenogram showed moderate atelectasis and no evidence of thymic enlargement. At necropsy numerous thrombi were found in the lungs with diffuse bronchopneumonia which proved to be of streptococcal origin. This must have been a prenatal infection.

He spoke also of secondary atelectasis as a cause of cyanotic attacks that occur after the first days of the newborn period.

Pneumonia due to aspiration of amniotic fluid was discussed and he felt it was more common than it is usually thought to be.

He cited a case of hemorrhage into the lateral cerebral ventricles which gave marked symptoms of respiratory difficulty. This case responded well to ventricular tapping.

DR. JOSEPH I. LINDE (NEW HAVEN CONN.) emphasized the importance of aspiration of amniotic fluid or other material as a cause of cyanosis, especially in those cases in which the cyanosis comes on a few hours after birth.

He stressed the advantages of the tent method of administering oxygen and carbon dioxide over the mask method.

There followed a discussion of different types of oxygen tents, especially of the one being demonstrated by the makers of the Drinker respirator

DR MARTIN M MALINER (BROOKLYN, N Y) asked if there was such a thing as delayed familial atelectasis. He cited the cases of three children in one family in which each had exhibited an almost identical clinical history after normal births they had shown intermittent attacks of cyanosis during the first two days, then had recovered, but after two months they each had an attack of dyspnea with cyanosis and fever. The physical and roentgenographic findings were those of atelectasis on the right side. Recovery occurred, but periodically such attacks would recur with the same findings. These children are now five, eight and ten years old, respectively.

CHAIRMAN PARMELEE—There is a condition called "congenital atelectasis," which gives exactly that clinical picture, but I know of no familial disorder of that sort.

DR MAURICE L RIPPS (ELIZABETH, N J) asked about the frequency of finding a patent ductus arteriosus associated with atelectasis also if concavity or angulation of the ribs was of value in diagnosing atelectasis.

He cited a case in which convulsions, crowing respirations, and spasmodic clenching of the hands might suggest spasmophilia, but he was of the opinion that cerebral hemorrhage was more likely the cause.

CHAIRMAN PARMELEE said that in his opinion every case of convulsions during the newborn period should be considered due to intracranial damage until definitely proved otherwise.

DR CHARLES A WILSON (DETROIT, MICH) —The ductus arteriosus is found to be patent in nearly all infants who die in the first week of life, and scattered areas of atelectasis are also usually found. It cannot be said that the atelectasis is related to the patent ductus. Areas of atelectasis are often found at necropsy in infants who have had intermittent attacks of cyanosis. It is very difficult to demonstrate these atelectatic areas in roentgenograms. Intracranial injury is found to be the cause of death in most of these cases. A large area of atelectasis that can be recognized roentgenologically may cause repeated attacks of cyanosis with recurrent attacks of fever over a period of years.

CHAIRMAN PARMELEE—It is natural that there should be some confusion in the application of such terms as cyanosis, atelectasis, asphyxia, etc. Disturbances which occur in setting into motion the respiratory mechanism must almost certainly affect the circulatory apparatus which is so intimately related to it and is itself undergoing a profound rearrangement in these first days of life.

The meeting was adjourned.

FIRST ANNUAL CLINICAL MEETING OF REGION III OF THE AMERICAN ACADEMY OF PEDIATRICS

The annual conference of Region III of the American Academy of Pediatrics was held Oct. 4 1934, at the Mayo Clinic, Rochester Minn. and Oct 5 and 6 1934 at the University of Minnesota Minneapolis.

The meeting was called to order by Dr Henry Helmholtz, chairman. Dr B W Carey acted as secretary.

REPORTS OF STATE CHAIRMEN

Ohio (Dr C W Burhans Cleveland)—The progress made by the Ohio committee during the past few months has been mostly in little things. Valuable contacts have been made with child welfare organizations and Parent Teacher Associations, and we have been asked to send a representative to their meetings.

Through the Ohio State Medical Association, we have cooperated in preparing diets for infants and children for use by the State Relief Commission.

The Bureau of Child Hygiene of the State Department of Health has been, because of financial reasons, without an active head for the past few years. What little work that was carried on was done largely by nurses. A civil service examination was given last spring and on July 1 Dr A L Van Horn was appointed as the director of this department. Dr Van Horn has been at the Babies and Childrens Hospital in Cleveland for the past three years and his appointment makes a very valuable contact between the Department of Health and the Ohio members of the Academy.

The postgraduate instruction in pediatrics to general practitioners has been progressing slowly. This is probably largely because of inertia on the part of the Ohio committee and especially its chairman, and partly because in sounding out the sentiment of the physicians in the state, it has not been possible to discover a great deal of sentiment in favor of it.

A further discussion of this question will take place at the meeting of the Ohio State Medical Association.

Michigan (Dr Bernard W Carey Detroit)—The report outlined the governmental activities for child welfare throughout the state as well as those of the volunteer agencies, pointing out the opportunity of Academy cooperation with existing programs.

The activity of Michigan members has been directed toward membership and the development of a postgraduate course for general practitioners in cooperation with the University of Michigan State Medical Society and the Detroit Pediatric Society.

The office of the state chairman has circularized the pediatricians of the state by letter in the interest of the American Board of Pediatrics and the meeting of the pediatric section of the State Medical Society. A special meeting was held to arouse interest in attendance at the Cleveland session of the Academy.

Indiana (Dr Oscar N Torian, Indianapolis) reported definite steps had been taken to form a state pediatric society and that an advisory committee to the State Health Department had been created and was functioning satisfactorily. Participation was reported in thirteen district postgraduate courses throughout the state. Work was

under way in the immunization program against diphtheria, and plans were under way for further activity in postgraduate instruction, immunizations, and a tuberculosis survey. Increased effort for members was also noted for the next year's program.

Minnesota (Dr E J Huenekeus, Minneapolis) reported splendid cooperation with both University and State Medical Society. Speakers are furnished to county medical societies for postgraduate instruction, and to Parent Teacher Associations. Effort is being made to bring preschool children into the doctor's office for examinations. Agreement was made to give twenty minute talks on periodic examinations before local parent teacher associations, and each cooperating P T A agrees to have each member assume responsibility for visiting ten families in an endeavor to have the children brought to the family doctor's office for health examinations. The physician charges his regular fee for these examinations.

Wisconsin (Dr Abraham B Schwartz Milwaukee) reported that the Medical Emergency Relief Program was under the direction of the executive secretary of the State Medical Society, and that this program was working satisfactorily. The Academy program was one of active cooperation with the County Medical Society. One meeting of state members of the Academy was held during the year.

Illinois (Dr Maurice L Blatt, Chicago)—Paper was submitted.

Iowa (Dr Lee F Hill, Des Moines)—The activities of the Academy have been linked up very closely with the State Medical Society and the State Department of Health. There is a committee designated as the "Committee on Child Health and Protection" and also a State Pediatric Society. The Academy works in close cooperation with both the above groups. These committees cooperating have to date set in operation a plan whereby all health programs of the state are referred to a committee in the local county so that the medical profession of the county is in close contact with, if not in charge of, the programs put on by the lay groups. This has not worked 100 per cent but is functioning much more smoothly than any previous system attempted. Also, the committee has reviewed all of the literature sent out from the Bureau of Maternal and Child Hygiene. This has tended to improve the quality and cut down the quantity of such distribution. Another matter which we have been interested in is the consent slip used in school immunizations by means of which an attempt has been made to send as much of this to the private physician as possible.

The committee has functioned further in relation to the state programs, and during the last annual meeting we were given one-half day of the three-day session. This year we held pediatric sessions on two afternoons. By cooperation with the Speakers' Bureau considerable information has been carried to the laity and practitioners from a pediatric standpoint.

Kansas (Dr Paul G Carson, Wichita)—Because of the very active political opposition on the part of the State Medical Society, and the small and widely scattered membership, activities of the members of the Academy in Kansas have, so far, been limited to educational talks to such organizations as the P T A., private schools, and a few radio talks.

This fall in Wichita we have finally been able to divorce the matter of immunization against diphtheria from the school physician and authorities. It is now to be done by the various individual physicians at the nominal fee of one dollar except in the case of those definitely indigent who are regularly receiving help from the county or city, in which cases, the county or city physician having constant contact and authority attends to it.

We hope to widen this very small opening wedge as rapidly as possible and ally ourselves, for the purpose of education, with all the public and private welfare organizations as well as educational organizations, the chief idea is to inform the public properly on the modern conception of the prevention of disease, with especial attention to the matter of contagious and infectious diseases and the matters pertaining to nutrition. We have also a ja andlometer and are testing the hearing of all school children in Wichita.

Nebraska (Dr Clyde N Moore Omaha) reports efforts along usual health lines the most important accomplishment being the formation of a Health Advisory Committee cooperating with the State Health Department.

Colorado (Dr F P Genjenbach Denver)—Besides the general work in child welfare carried on by Colorado members of the Academy, the most recent activity has been in a survey of crippled children in the state.

South Dakota (G E Zimmermann Sioux Falls) reported little activity due to lack of cooperation of the Department of Health.

Missouri (Dr T C Hempelmann, St Louis) had no report.

North Dakota (Dr E E Pray Fargo) had no report.

New Business—Dr Clifford G Grulec, secretary-treasurer of the Academy reported that

The 1935 annual meeting will be held at or near New York City on June 7 and 8 the Friday and Saturday preceding the annual meeting of the American Medical Association to be held at Atlantic City. An attempt to secure special rates for the Academy meeting on all railroads is being made.

Dr Grulec reported briefly on the work of the various committees.

A question was raised as to the wisdom and desirability of holding the Academy's meeting near the time of the American Medical Association meeting. The thought was expressed that the length of time consumed by the two meetings was prohibitive and would react on attendance at the Pediatric Section of the American Medical Association. Three members spoke on the desirability of holding the meeting entirely distinct from the American Medical Association session. The question of passing a resolution to this effect for submission to the executive committee of the Academy was mentioned but no action taken.

The following officers of Region III were elected for 1935: chairman of clinical meeting A. Graeme Mitchell, M.D. Cincinnati, Ohio; vice-chairman, Albert J. Bell, M.D., Cincinnati, Ohio; secretary and editor Jacob V. Greenebaum, M.D. Cincinnati, Ohio.

Next year's clinical session will be held in St. Louis, Mo., in November. This will be a joint meeting with Region II at the time of the annual meeting of the Southern Medical Association.

A motion that a message of best wishes for a speedy convalescence to Dr. Bell who is ill, was passed.

A motion that the thanks of the session be extended to the Mayo Foundation and the University of Minnesota for the courtesies extended during the meeting was passed.

At a luncheon meeting of state chairmen, it was decided to create a committee composed of the chairmen from Iowa, Indiana, Illinois, and Michigan, who would formulate a program for state activity. This program will be discussed at a meeting of state chairmen held during the annual meeting.

ABSTRACTS OF PAPERS PRESENTED OCTOBER 4 IN THE SESSIONS
AT THE MAYO CLINIC**Intestinal Polyposis. Harry M Weber, M.D., Rochester, Minn.**

Adenomas or adenomatous polyps, the histologic types that are most frequently encountered, increase in frequency from the upper part of the intestinal tract downward. They may be single or multiple and scattered sparsely or densely throughout the intestine. "Polypoidosis" refers to that condition in which the entire mucosa seems to have been transformed into a villous, convoluted mass of adenomatous tissue.

When polypoid lesions occur in any part of the large intestine, the rectum and lower portion of the sigmoid flexure will be involved in about 95 per cent of instances. Therefore, digital and proctoscopic examination will discover the vast majority of these lesions. Roentgenologic examination of the colon will determine the extent of polypoid involvement and demonstrate the presence or absence of polypoid lesions in segments of the intestine, which are beyond the reach of the examining finger and of the proctoscope. Unless they are large, ordinary roentgenologic examination does not demonstrate polypoid lesions. A method especially useful for this purpose is briefly as follows:

After the intestine has been thoroughly cleansed of fecal material, gas, fluid, and secretion by catharsis and enemas, the opaque enema is given in the ordinary manner under roentgenoscopic control. The patient is then permitted and urged to evacuate this enema as quickly and as completely as possible so that only a thin coat of opaque material remains adherent to the mucosal surface of the intestine. Again, under roentgenoscopic control, the intestine is redistended with air or some other inert gas. Stereoscopic roentgenograms are then made. This technic provides what might be called a transparent media. The internal surface of the lumen of the intestine is brought out in bold relief, and the recognition of these polypoid excrescences becomes a relatively easy task provided the rather complicated technic has been carried out properly. Because it is complicated, however, the application of this method to young patients, who are unable to give the same degree of cooperation expected from adults, is often difficult. When satisfactory roentgenograms are obtained, the diagnosis of small nondeforming intraluminal lesions in the large intestine is second in precision and accuracy only to direct examination with the proctoscope, surgical exploration, or necropsy.

Eosinophilia (Case Report) Laura M Fisher, M.D., Rochester, Minn.

The child showed enlargement of the liver and spleen.

Examination of the blood showed hyperleucocytosis and eosinophilia. The highest leucocyte count was 104,000 per cubic millimeter, with 81 per cent eosinophiles.

As the child's health improved, the number of leucocytes and eosinophiles decreased, the percentage of hemoglobin increased, the liver and the spleen gradually became impalpable, and the general condition of the child improved.

A number of cases, in which the values for the eosinophiles were as high as 95 per cent, have been reported. Biopsy was performed in some of these cases, and others came to necropsy. Some of the cases were diagnosed as myelogenous leukemia, Hodgkin's disease, and pernicious anemia, while others were classified as eosinophilia with hyperleucocytosis.

The condition, which has been described in the case history, does not correspond with the other cases, which have been reported in the literature. In view of the longevity of the patient, the progressive improvement, and the comparative well being, even during the stage when the number of eosinophiles were high, no definite

diagnosis made, and the condition has therefore been classified as a chronic blood dyscrasia with hyperleucocytosis and eosinophilia.

Study of Organ Hypertrophy Frank O Mann, M.D. Rochester Minn.

Partial or complete restoration of the amount of tissue lost by removal occurs in most, but not in all, of the organs of the body after partial removal. This restorative process has been called physiologic compensation. There is a considerable variation in the different organs in the amounts of tissue restored and in the rate at which restoration occurs. In our experiments, splenic tissue is not restored after partial removal. There is usually very little restoration of thyroid tissue after partial thyroidectomy. The most marked restoration has occurred in the liver, kidney, colon, and stomach.

Seventy per cent of the liver can be removed from a rat and complete restoration of the amount of tissue lost will occur within six to eight weeks. One kidney can be removed from a rat, and eight to ten weeks later the remaining kidney will have increased in size almost enough to equal the renal tissue removed. Two-thirds of the colon of a dog can be removed and a year and a half later the capacity of the remaining portion will almost equal that of the whole large intestine at the time of removal. All the stomach of a dog except a small rim around the cardia, can be removed, and at the end of four years normal gastric capacity will have been restored.

The causes and mechanism producing restoration after partial removal are probably not the same for all organs although there are some common factors. It would appear that while considerably less than half of the normal amount of the various organs is sufficient to maintain life, a more nearly normal amount is necessary to take care of the peak load of functional activity which may be placed upon them. There also appears to be one factor common to all organs undergoing physiologic compensation, namely an increased blood flow to the organ involved.

Considerable data have been accumulated in support of the theory that restoration of an organ, after partial removal, is owing to a physiologic need for a larger functional capacity of that particular organ. All functions of an organ, however, are not of equal value in causing a restoration of an organ. Our experiments would indicate that the function of furnishing a portal pathway is the most important of the various functions of the liver in causing restoration of that organ to occur after partial removal. On the other hand excretion of the nitrogenous products of the urine is the most important function of the kidney in causing compensatory hypertrophy to occur in that organ.

Rocky Mountain Spotted Fever Robert S. McKean, M.D., Rochester Minn.

There is evidence that the area in which Rocky Mountain spotted fever may occur is increasing and because this disease has a rapid onset with headache, chill, fever, pains in the muscles and joints and subsequent muscular eruptions, it may simulate some of the exanthematous fevers. Two cases of Rocky Mountain spotted fever which were observed at the Mayo Clinic during the past year are reviewed. Both cases were treated expectantly and uneventful recoveries ensued.

Disturbances of Function of the Thyroid Gland. Roger L. J. Kennedy M.D., Rochester Minn.

Disturbances in function of the thyroid gland of children are not especially uncommon. Both hyperfunction and hypofunction occur but there appears to be

some misunderstanding over what constitutes examples of each. In children symptoms of exophthalmic goiter are quite similar to those in adults and are sufficiently striking to warrant a reasonably early diagnosis

One hundred and fifty seven cases of exophthalmic goiter among children admitted to the Mayo Clinic have been studied. During the period of time in which these were seen, no instance of any other type of hyperfunction of the thyroid gland in children was observed. It would appear, therefore, that the terms "hyperthyroidism" and "thyrotoxicosis" are not only unnecessary but even incorrect when applied to children, as they do not indicate accurately the condition present, namely, exophthalmic goiter. Thyroid tissue in cases in which resection of the thyroid gland was carried out in all but two cases showed diffuse parenchymatous hypertrophy, thus substantiating the clinical diagnosis of exophthalmic goiter.

Hypothyroidism

Insufficiency of thyroid secretion among children varies in its manifestations, depending on the stage of development of the individual at the time when deprivation begins.

Endemic Cretinism—Endemic cretinism, rare in this country, is a condition in which deprivation begins even before intrauterine development starts. One or both parents lack sufficient thyroid secretion.

Athyrotic Cretinism—Athyrotic cretinism is a condition in which the thyroid gland either fails to appear or fails to develop and in which the child, during intrauterine life, receives its supply of thyroid secretion from the mother. Such children begin to show the effects of a lack of thyroid substance from six to eight weeks after birth. Supplying such a child early and continuously with a potent thyroid preparation will result in practically normal growth and physical development, but will probably not result in normal mental development.

Infantile Myxedema—Infantile myxedema is a condition in which deprivation of the thyroid secretion does not take place before the infant has undergone an appreciable development under the influence of adequate thyroid secretion.

Juvenile Myxedema—Juvenile myxedema is a condition in which the lack of thyroid secretion is not marked before the child is two years of age. In these cases, recognition of the condition and proper treatment will usually restore the status of the individual to near normal, the result to be expected in treatment of adults who have myxedema.

Infantile Muscular Dystrophy John J. Slavens, M.D., Rochester, Minn.

Case reports of two sisters present rather unusual conditions, which are almost identical, differing only in degree. The weakness and wasting are universal, excluding only the facial and bulbar muscles. In the case of the older child, the speech has been affected despite the absence of weakness of the muscles involved in the act. Mastication and deglutition have not been affected. All the reflexes are present, the sensorium is unchanged, and the mentality is normal. There appears to be a uniform wasting of muscle tissue with absence of fibrillary twitchings.

Muscular dystrophy usually begins between the second and seventh years and frequently reveals pseudohypertrophy. In the present cases, the weakness is uniform. The children lack the characteristic attitude and gait, the symptoms began at an earlier age and progressed much more rapidly than in muscular dystrophy. However, it is felt that the condition affecting these two sisters is one of infantile familial muscular dystrophy.

Crystalline Cortin. Edward O Kendall, Ph.D. Rochester Minn.

The amount of cortin in the suprarenal gland is equal to approximately 1 per cent of the epinephrine in the same weight of gland. The amount of epinephrine present averages somewhat less than 0.2 per cent of the wet weight of the gland. Thus, less than 0.002 per cent of the wet weight of the gland is cortin. The amount of cortin in both glands of a beef is about 0.5 mg and the weight of cortin in a single gland is therefore approximately 0.25 mg

We have found that, after complete suprarenalectomy, dogs can be maintained in normal condition in respect to body weight and all other criteria which can be applied. The daily requirement for each animal can be determined by administration of the solution. In each case a certain minimal amount must be given in order to maintain the animal.

A patient who had a severe case of Addison's disease was maintained for eighteen days by administration of about 10 mg of crystalline cortin each day without development of signs of insufficiency. Finally a dog which was suprarenalectomized by Dr Mann was given the crystalline hormone during the eight days following operation. The dog received no other form of medication and survived the operation and appeared to be entirely normal at the end of eight days. He was placed on a high salt diet and has lived for several months.

We have, furthermore, found that the cortin in crystalline form is quite insoluble in water one part will dissolve in about 10,000 parts of water. There is present in the solution however a more soluble form of the hormone which will exert the same physiologic effect and, as far as can be determined, the weight of material in soluble form is the same as the weight required in crystalline form. The exact relation between the two forms has not yet been established, but the essential groupings appear to be aldehyde and hydroxyl groups. There is no change in molecular weight when the hormone assumes the less soluble form.

The problem of the chemical nature of the suprarenal cortex has now been reduced to a concrete problem in organic chemistry. We may feel certain that in the near future the structure of the crystalline hormone will be established after this has been accomplished, we shall be in a position to know whether or not this complex substance can be made synthetically.

Benzol Persulphide Dusting Powder to Relieve Itching. Samuel Amberg M.D., and Louis A. Brunsting M.D. Rochester Minn.

A substitution of sulphur for oxygen in the molecule of benzol peroxide might be of value in some forms of cutaneous infections. After a consideration of benzol peroxide as a hydrogen peroxide in which the hydrogen atoms are replaced by benzol groups, benzol persulphide may be regarded as a similar substitution product of hydrogen persulphide that is the reason for its name.

Benzol persulphide can give off sulphur which may be transformed to sulphuretted hydrogen, of which 25 per cent of the weight of the persulphide can be formed. Sulphuretted hydrogen is not a harmless substance. From the intact skin it does not seem to be absorbed but from an injured skin it may be absorbed. In infants it is said that sulphur ointment for scabies has led to intoxications with sulphuretted hydrogen, which did not result from inhalation. With the relatively small amounts of persulphide used, it is very unlikely that conditions of danger would be realized nevertheless such a danger cannot be disregarded entirely. The substance is insoluble in water but soluble in some organic solvents, particularly in carbon bisulphide and in sulphonated bitumen (ichthyol).

We compared the effects on poison ivy dermatitis of talcum, powdered benzoic acid, benzol peroxide and benzol persulphide, rubbing these substances lightly into the skin. Talcum was without effect, benzoic acid had a slight and rather transitory effect, and later became irritating, while benzol peroxide and benzol persulphide were equal in their activity. This activity consisted in allaying the severe itching for from four to six hours, making sleep possible. The dermatitis itself was apparently not influenced. For a few minutes after the application the itching was not relieved or became even worse, after five to fifteen minutes, it ceased.

In some cases the full strength powder was irritating. The powder should be very fine. In these cases, at the start, ointments cannot be used, in later stages the substance can be used as ointment. We may say in ointment form we prefer the peroxide, which has some bacteriostatic action, which persulphide has not.

On some cases of insect bites, the substance was also efficient, such as the bites of sand fleas and mosquitoes. It also proved of value in a few cases of pruritis of the anus or vulva. In such cases the rubbing in of the powder may prove irritating, particularly if it is too gritty or if too much is used so that it cakes. These difficulties may be avoided. It proved inefficient in eczema and extensive allergic conditions of the skin with itching.

Partial Obstruction Resulting From Ileitis Donald L. Gillespie, M.D., Rochester, Minn.

This case is an instance of inflammation of the small intestine. A boy had been ill for three and a half months with abdominal pain, fever, and tarry stools and was progressively growing weaker.

An exploratory laparotomy showed ileitis with partial obstruction.

Neuronitis Frederick P. Moersch, M.D., Rochester, Minn.

Neuronitis, which has been described under various headings, may affect children. The clinical history is fairly typical. The findings may vary somewhat as to their location and severity. The most characteristic symptoms are reviewed. The importance of examination of the spinal fluid is emphasized as these findings may aid in establishing a definite diagnosis.

Some Experimental and Therapeutic Applications of Artificially Induced Fever Charles Sheard, Ph.D., Rochester, Minn.

Experimental Data—In this paper are presented results obtained with relatively short electric waves (75 to 20 meters) produced by a General Electric radiotherm having an approximate output of 150 to 400 watts. The experimental data obtained with *systemic* applications of high frequency energy show that in the living animal (dog) muscle tissue is affected slightly more than is subcutaneous tissue, intraarticular temperature is affected more than is muscle tissue. The reaction of anesthetized animals to general body hyperthermia with this agent is quantitatively different from that of the unanesthetized animals. Temperature measurements on the tissues of dead animals have shown that bone is heated much more markedly than is muscle tissue and have indicated that the temperature changes produced by the electric field are strictly dependent on the position and composition of the various tissues. By the employment of *local* applications of the short wave electric field (through the use of small condenser plates), there has been demonstrated the importance, therapeutically considered, of the relationship between the heat developed in deep lying and superficial tissues, respectively, as dependent on the distance at which the condenser plates are placed with respect to the surface of the tissues.

By suitable procedures it is possible to produce relatively high temperatures in a chosen region (such as the knee joint of a dog) by means of local applications of short wave energy of sufficient intensity. Furthermore these temperatures may be produced in the deep (intra-articular) tissue of the region without the production of appreciable increases in the superficial (subcutaneous) tissues of the region. Local applications in selected types of clinical cases have proved beneficial.

Clinical Application.—The therapeutic applications were carried on with two types of artificial fever equipment (a) Kettering-Simpson, employing humidified air heated over electric strip-heaters and circulated in the closed chamber and (b) incandescent lamps (infra red radiation) operated and controlled electrically to produce the necessary environmental temperature. The rectal temperature of the patient using either method is raised rather slowly but steadily to the rectal temperature desired. This temperature ranges from 103.6° F. to 107° F., depending on the type of disease under treatment. The desired rectal temperature is maintained as uniform as possible for five hours. Treatments are repeated when found desirable or necessary.

From the data presented the conclusions are drawn that 1. The conception that fever is a destructive process only is being supplanted by proof that fever is a protective and defensive mechanism. 2. The value of induced fever is being established since the result obtained in the treatment of syphilis, gonococcal infections, and arthritis can be attributed largely to the production of fever. Whether the effects of radiotherapy and other means of producing artificial fever are comparable in all respects is a moot question. 3. Artificially induced fever is apparently very beneficial in all types of Neisserian infection and has been demonstrated to achieve outstanding results in conditions of early neurosyphilis.

Treatment of Progressive Muscular Dystrophy With Glycine. Walter M. Boothby M.D. Rochester Minn.

We have had twenty seven cases of progressive muscular dystrophy under treatment with glycine for between eight months and twenty six months. This series includes examples of all the various types of the disease and the patients vary in age from two and a half to fifty years.

Unlike the marked improvement that we obtain in many cases of myasthenia gravis, in these cases of progressive muscular dystrophy we have only obtained a general improvement in health, decrease in fatigability and possibly a decrease in the tendency to taking cold easily. We have not obtained any evidence of a definite recovery in the function of a muscle the ability of which to contract was markedly repaired. The general improvement of the patient and the decrease in fatigability which allows the patient to be more active all day long must be distinguished sharply from an actual improvement in the condition itself and the regaining of any muscle function which actually has been lost. We believe that glycine is valuable in progressive muscular dystrophy for two purposes (1) to decrease the fatigability and thus permit the patient to do more throughout the day and (2) to improve the general nutritional condition in the hope that this improvement will retard the advance of the disease. In those cases in which this can be accomplished it is a great and real benefit. In explaining this possibility to the patient, it is necessary to avoid raising false hopes of curing the disease or suggesting that muscle tissue which actually has been destroyed can be regenerated.

Planning the Ketogenic Diet. Mary A. Foley Rochester Minn.

The ketogenic diet must be planned to meet the individual need. The calories required for the daily intake may be calculated by means of the Boothby-Berkson nomogram (Chart 1)

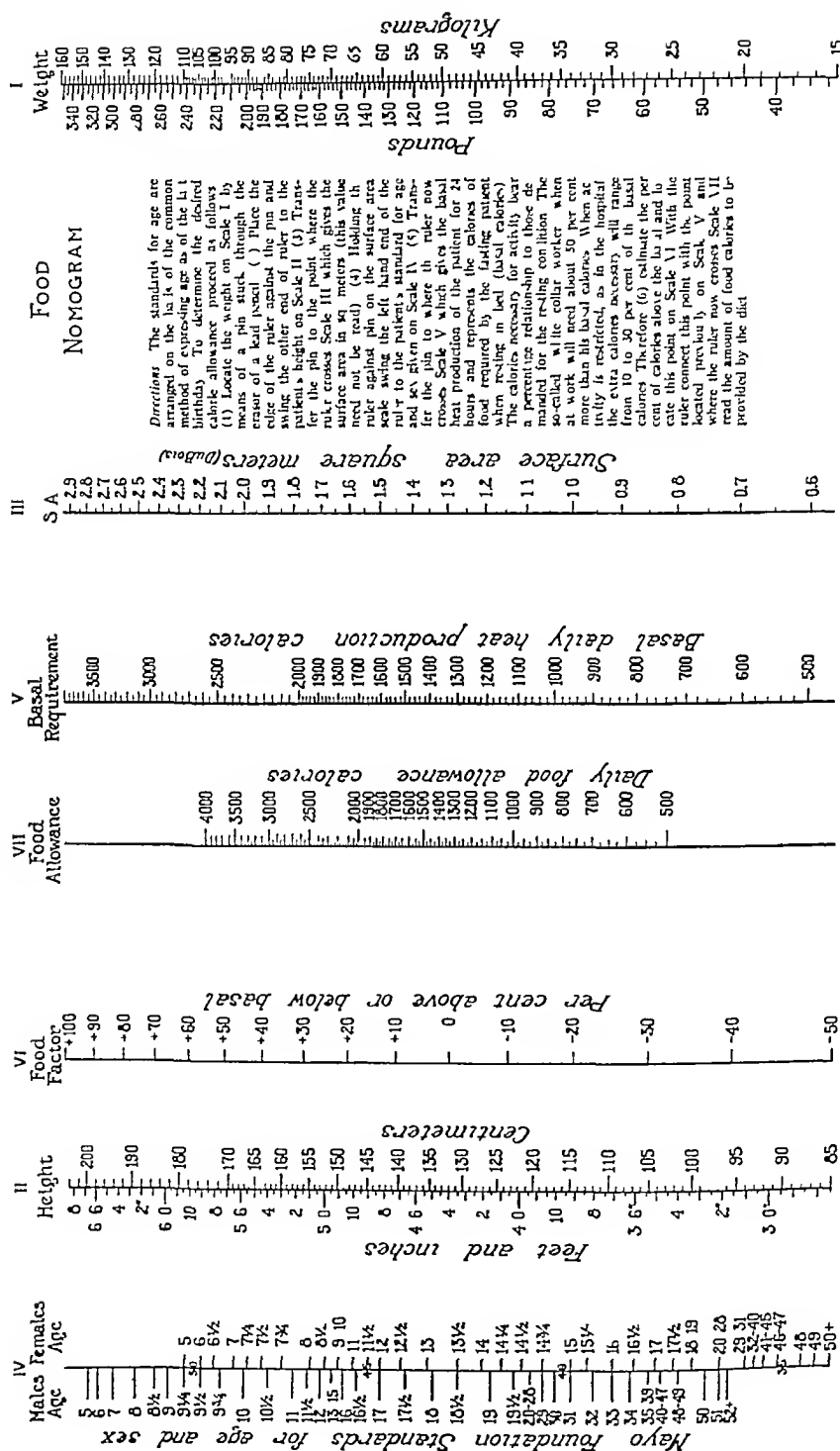


Chart 1

With this material as a working basis we make our daily menus. A ketogenic diet in itself is not very interesting, and it requires much ingenuity to make it palatable.

A day of starvation is helpful in some cases. The ketogenic diet must be followed strictly. There are no halfway measures.

Constipation is a factor which must be considered in the management of the patient who is receiving a ketogenic diet. Many of the cathartics ordinarily prescribed contain sugar in some form.

The change from the high carbohydrate and moderate fat diet to the low carbohydrate and high fat diet occasionally results in nausea, vague pains, and loss of weight and strength. If nausea persists, a small amount of orange or tomato juice is helpful. The loss of weight which varies between 3 to 5 pounds, is the result of dehydration. Adjustments are made within a week or two and the weight, which has been lost, is regained.

The Use of Ketogenic Diet in Urinary Infections Demonstration of Determination of Necessary Concentration of Beta-Oxybutyric Acid and pH of Urine. Arnold E. Osterberg, Ph.D. Rochester Minn.

It is important in prescribing the ketogenic diet to know more accurately the pH value and the concentration of beta-oxybutyric acid in the urine. The knowledge of these two factors is essential in determining whether the diet is being assimilated and metabolized to produce a urine which will be bactericidal. Hence it is of distinct advantage to the clinician to have at his disposal simple procedures by which he is able to know for certainty these factors.

We have adapted the Rothera test by which it is possible to determine within a few minutes whether or not the concentration of beta-oxybutyric acid is greater or less than 0.5 per cent.

By the use of this simple procedure the clinician is enabled to know in a few minutes and with a minimum amount of urine whether or not the ketogenic diet is efficient. For more accurate knowledge of the concentration of beta oxybutyric acid that is being obtained, one should determine its concentration in several specimens of urine which have been collected at different intervals during the day. This is for the reason that the concentration of beta oxybutyric acid varies with the length of time subsequent to the ingestion of the fatty meal. By the use of these tests we feel that the clinician should know accurately the effectiveness of this type of diet and whether or not the ratio of fat, carbohydrate, and protein should be varied to effect greater efficiency and that guesswork is removed from this type of therapy since one cannot expect bactericidal action to be present unless these standards have been met.

The Clinical Results of Ketogenic Diet Therapy Henry F. Helmholz, M.D., Rochester Minn.

The ketogenic diet has been used in thirty-seven cases in which the patients were suffering from urinary infections. In the use of the diet early in our experience we were in doubt as to what were the conditions necessary to bring about a cure, and only after an experimental and clinical study did we come to the conclusion that two conditions are necessary in order that a urine may have a bactericidal action first, that the pH of the urine must be 5.5 or below; and second, that the concentration of beta-oxybutyric acid must be 0.5 per cent or greater. If a pH of 5.5 or less and 0.5 per cent concentration of beta-oxybutyric acid are present, it is safe to say that the urine will act bactericidally on *Escherichia coli*, *Bacillus proteus*, *Aerobacter aerogenes*, *salmonella*, *pseudomonas*, *Streptococcus fecalis*, *Streptococcus hemolyticus*, *Staphylococcus albus*, and *Staphylococcus aureus*.

From our experience we find there are four conditions that may interfere with the success of the diet (1) the functional incapacity of damaged kidneys to excrete a urine of low pH and high beta oxybutyric content, (2) the inability of the individual to digest the amounts of fat fed with the result that large amounts of fat are found in the stool and necessary ketosis never is achieved, (3) the inability of the patient to take the amounts of fat necessary to produce adequate ketosis, and (4) the presence of stones in the urinary passages

Contrary to the experience of others, in eight of the sixteen cases in which there was stasis, it was possible to sterilize the urine and the urine remained sterile after the treatment was discontinued. In a number of cases there was a return of the infection at a later date, this does not discredit the method but indicates that conditions were such that reinfection was likely to occur. Whenever possible, the cause of the stasis must be removed

Reducing Diets in Children. Russell M Wilder, M D, Rochester, Minn

It has been said that obesity in childhood always indicates an underlying endocrine abnormality. The dictum is based on the fact that children who are fat resemble in some respects the clinical picture that is frequently referred to as the Frohlich syndrome. It is apparent, however, that this resemblance is a superficial one. These children are too young to have developed sexually. However, give them time to grow, and nearly all of them reveal normal genitals, reduce them by proper dieting and the last resemblance to the Frohlich syndrome disappears.

It is often stated that the obese child is difficult to reduce. This has not been true in my experience. He loses fat readily if the intake of food is rigidly supervised and made less than the total expenditure of energy. A plan for reducing is described which is based on the procedure advocated by Strang, Evans, and McCuggage and which has proved very satisfactory in my hands. It involves limiting the calories in the food to about 550, providing adequate protein, with particular reference to protein of high biologic value, and supplying extra vitamins as concentrates together with extra calcium phosphate. The rate of loss of weight on this regimen will vary depending on the original weight of the individual. It is as rapid as is theoretically possible, however, and the patients usually feel perfectly well. Probably because they are actually not underfed in any particular except calories, the patients on this diet do not tend to break the diet by surreptitious eating. A successful reduction is thus usually accomplished.

Indications for Sympathectomy in Hirschsprung's Disease Alfred W Adson, M D, Rochester, Minn

The correction of Hirschsprung's disease is a neurosurgical problem of reestablishing normal peristaltic movements and regulated periods of defecation. The surgical attack on the sympathetic nerves of the colon, sigmoid, and the internal sphincter of the rectum has produced satisfactory results. It is apparent that the inhibitory muscular responses of the colon, and the contracting stimuli to the internal sphincter of the anus from the sympathetic outflow are more powerful than the motor responses of the musculature of the colon and the inhibitory responses to the internal sphincter of the anus, which come from the parasympathetic nerve supply. Defective parasympathetic innervation might produce a similar effect since the emptying stimuli would be less than the filling and retaining stimuli.

Surgical Indications and Preoperative Preparation.—Surgical intervention is not instituted in the mild cases of Hirschsprung's disease in which medical treatment is adequate, but if it becomes necessary for the patient to return to the hospital more

than two or three times for emptying of the colon and the employment of a still more rigid regimen, sympathectomy is indicated. The administration of acetylcholine which inhibits the activity of the sympathetic nervous system, has served as a pre operative test in selecting patients for sympathectomy.

Sympathectomy now includes a resection of both lumbar trunks with the second, third, and fourth lumbar ganglions, and a wide resection of the superior hypogastric plexus, the presacral nerve situated on the promontory of the sacrum in the triangular space below the bifurcation of the abdominal aorta. This procedure is employed to include all of the sympathetic fibers from the lumbar chain all of the intermesenteric fibers, descending into the pelvis below the inferior mesenteric artery, and those fibers, which rejoin the hypogastric plexus from the inferior mesenteric nerve in the mesocolon of the pelvis thus leaving only a small group of fasciculi which have followed the inferior mesenteric artery and its branches to the lower part of the colon, and the internal sphincter of the anus.

Chronic Ulcerative Colitis Among Children. J. Arnold Bargen, M.D., Rochester Minn.

Between 1929 and 1934, thirty-nine children who had chronic ulcerative colitis were observed at the Mayo Clinic. Seven of these children were twelve years old. The other thirty-two children were between two and fifteen years old. On the regimen outlined twenty-one of these patients are today clinically well, two are free of symptoms and have not had any recurrence of the trouble, five are improved at least 50 per cent, five are under active treatment, two are no better, and four have died of perforation, hemorrhage, extensive thrombophlebitis, or liver abscesses.

Preoperative Roentgenization of Tumors of the Kidney. Arthur U. Desjardins, M.D., Rochester Minn.

Among the tumors of the kidney the most common are adenocarcinoma, which frequently affects adults on the basis of an established simple adenoma, embryonal tumors of the kidney affecting adults, and embryonal tumors among children or as Ewing calls them embryonal myosarcomas.

The one renal tumor which is distinctly radiosensitive is the embryonal myosarcoma or mixed tumor so common among children, and to which the name of Wilms is frequently attached. The radiosensitiveness of these tumors is almost as great as that of lymphosarcoma. Unfortunately while the primary tumor can usually be made to retrogress substantially so that in some cases it may even seem to disappear as far as clinical examination goes, few such tumors have been cured permanently by irradiation or by any other method. For a number of years some of the cases encountered here at the Mayo Clinic had been treated with roentgen rays only, while others had been operated on and an attempt made to remove the tumor. Neither of these two methods has yielded satisfactory results as far as cure or prolonged improvement is concerned.

During the last year or two we have been trying a new method and this is to treat such tumors with roentgen rays, and after a certain interval (three to eight weeks) to remove the residual tumors by surgical means. It is too soon to know whether this combined method will yield results sufficiently superior to the methods previously tried to make it stand out as a definite advance in therapeutics. On theoretical grounds the results should be better.

It is possible that the Coutard method may prove a distinctive advantage. However inasmuch as these tumors affect children and often occur in very young children the possibilities of the Coutard method will have to be considered with con-

siderable care and judgment with reference to each individual case because this method is one which should be applied only to cases in which the general condition of the patient is still good and in which the patients can tolerate daily exposure to the rays for a sufficient length of time to build up a very large total dose. Therefore, it should be reserved for cases in which the tumor is not too large and in which complications have not set in. Otherwise, I fear that, instead of yielding improved results, the method might prove a detriment, at least to a certain percentage of patients. Another point in connection with the Coutard method is that it cannot be repeated more than once, and this only after a rather long interval (three to six months). In other words, it is a method designed to bring about a cure and should be reserved for cases in which a cure is at least within the realm of possibility. In cases in which such a possibility is out of the question, the patient should not be subjected to the Coutard method but should be treated with a different technic and with the idea of bringing about maximal improvement and yet preserving the possibility of repeating the treatment later, if this should be necessary.

Application of New (Mayo Foundation) Standard for Basal Metabolic Rates in Children With Exophthalmic Goiter Roger L. J. Kennedy, M.D., Rochester, Minn.

Over a period of time, data have been accumulating in the metabolism laboratory of the Mayo Clinic which have been employed by Boothby and his associates in the construction of a new standard for the determination of the basal metabolic rate. A sufficient number of children of the various age groups have been studied to supply data upon which a curve of metabolic rates has been constructed, which is thought to be more reliable than those previously constructed. The use of the new Mayo Foundation standard in determining the basal metabolic rates of children who had exophthalmic goiter has brought out some interesting facts.

One hundred and fifty-seven children who had exophthalmic goiter have been admitted to the clinic in the past twenty-five years. Determinations of the metabolic rates have been made on most of the children admitted with this disorder since 1917. Until very recently, the DuBois standard has been followed, but for purposes of comparison the rates have been calculated by both the DuBois and the Mayo Foundation standards. These calculations have been studied biometrically, and curves, which represent the percentage frequency, have been constructed to demonstrate the distribution of the rates as determined by each standard.

Those children with exophthalmic goiter, who received no iodine previous to admission, showed high basal metabolic rates as determined by either the DuBois or Mayo Foundation standards. In some cases in which a clinical diagnosis of exophthalmic goiter was made and in which pathologic examination, following operation, revealed a diffuse, parenchymatous hypertrophy of the thyroid gland, it was found that the basal metabolic rates were surprisingly low when the customary (DuBois) standard was followed. Calculated by the new standard, this group is eliminated or else is very small, indicating that in this respect the new standard reflects more dependably the rate characteristic of the disease. If the group is considered as a whole and the mean value for the basal metabolic rate is computed, it is found to be higher by the new standard than by the old standard. According to the new standard, the mean value in a group of seventy children was +41.9 as compared to a mean value of +33.9 for the same group by the DuBois standard.

In the second group, those who received some iodine previous to their admission to the clinic, the same fact is evident. The lowest basal metabolic rates were those

which were calculated according to the DuBois standard, and the mean value for the group was found to be lower +28.0 by the DuBois formula as compared to a mean of +33.0 when the new standard was employed.

It is evident also, in this group of children, that the administration of iodine had a definite effect on lowering the basal metabolic rates. When the mean values for this group and the first group were compared a decrease of nearly 9 per cent was found.

In the third group those who received intensive iodine therapy the same facts concerning a comparison of the two standards were plainly revealed. There was a tendency for the DuBois values to be lower than the Mayo Foundation values and a very definite difference in the mean values by the two methods. Not only has this study revealed comparable facts concerning the two standards but also the striking effect of the administration of iodine to children who have exophthalmic goiter has been demonstrated. The mean values for the basal metabolic rates of those who received iodine in adequate amounts were reduced from +41.9 to +31.4 a reduction of 20+ per cent.

Equally interesting no doubt, will be a study of a good sized group of children suffering from hypothyroidism and a group of children who have obesity of the constitutional type, as well as those who have obesity of types that have been ascribed to dysfunction of the various endocrine glands. It appears likely that such a study will result in some definite alteration of basic conceptions regarding these conditions.

Demonstration of New Scales. Samuel Amberg, M.D., Rochester Minn.

The platform of the scales is replaced by a metal beam, which is high enough to allow the scoop to be suspended from it, thus insuring a stable equilibrium. A few short chains are attached to the scoop and to the suspension beam to prevent tipping from side to side and forward while the nearness of the scoop to the suspension beam prevents tipping backward. The scoop is very readily accessible.

The Suprarenal Cortical Syndrome Resulting From Cortical Tumors. Waltman Walters, M.D., Rochester Minn.

In the past two years, since the advent of active preparations of the suprarenal cortical hormone eight patients presenting the suprarenal cortical syndrome have been operated on at the Mayo Clinic with one death from apparently accidental causes. Although considerable variation may be encountered the syndrome is generally characterized by hirsutism, amenorrhea, hypertension and hyperglycemia, and by obesity of the face, trunk and abdomen. Acneiform eruptions, cutaneous infections and osteoporosis have also been common symptoms. Surgical removal of the suprarenal cortical tumors was followed by rapid return to normal of previously abnormal physical metabolic conditions.

Of particular interest was one patient aged nine years who presented all of the characteristics of the lesion, with what was found to be an encapsulated tumor measuring 6 x 4 x 2 cm., which was removed from the left suprarenal gland Oct. 30 1933. Her return to normal appearance and normal physiologic conditions has been striking. The case is so interesting that a complete resume of the history is given.

Chronic Dyspnea and the Thymus in Infants and Young Children. Gordon B. New M.D. Rochester Minn.

A diagnosis of enlarged thymus should not be made without a laryngoscopic examination to exclude the possibility of some conditions which have been described as being the cause of chronic dyspnea, such as congenital laryngeal stridor bilateral

median line postoperative vocal cord paralysis, neoplasms, congenital subglottic diaphragm, lingual thyroid, and obstruction of the posterior nares. Enlarged thymus, with the exception of neoplasms of the thymus, can seldom be the cause of death, which results from respiratory obstruction. There has been no death attributed to hypertrophy of the thymus which has occurred during or after operation in infants and young children. No treatment has been given for enlarged thymus in any case.

Postoperative Thrombophlebitis of the Inferior Vena Cava. Charles E. Ward, M.D., Rochester, Minn.

A case of postoperative thrombophlebitis of the inferior vena cava in a child is reported because of the recovery of the patient and his almost complete compensation for the total occlusion of the main venous trunk.

Following an operation for removal of a gangrenous appendix on the ninth day of an otherwise uneventful convalescence, the left lower extremity became very painful, markedly swollen, and edematous. Pulmonary infarction was suspected on the twelfth day because of cough, and pain in the left axilla. On the fifteenth day the right lower extremity went through the same sequence of events previously noted in the left, thus indicating complete obstruction of the lower inferior vena cava.

The fever, swelling, and edema of the lower extremities gradually subsided in the course of eight weeks.

ABSTRACTS OF PAPERS PRESENTED OCTOBER 5 AND 6 IN THE SESSION AT THE UNIVERSITY OF MINNESOTA

Hepatonephromegalia Glycogenica—Glycogen Storage Disease of von Gierke. Robert L. Wilder, M.D., Minneapolis, Minn.

Enlargement of the liver and kidneys due to excessive storage of glycogen was first reported by von Gierke in 1929. Since that time, sixteen additional cases have been reported. Findings of the case reported show that this is a case of glycogen storage disease, that the liver lacks ability to store excess intravenous saline, and that this disturbance may be due to hypophyseal or hypothalamic disturbance.

(To appear in full in the JOURNAL)

Effect of High Sodium Chloride Ingestion on Blood Pressure and Carbohydrate Metabolism in Diabetic Children. Willis H. Thompson, M.D., and Irvine McQuarrie, M.D., Minneapolis, Minn.

In the course of a study of the factors involved in the abnormal craving for salt manifested by a severely diabetic boy, it was observed that the daily ingestion of between 60 and 80 grams of NaCl caused a marked elevation of blood pressure and a significant decrease in glycosuria. These observations were made repeatedly while the patient was maintained on a standard diet and received a uniform dosage of insulin gauged at such a level as to permit a moderate degree of glycosuria at all times. Ingestion of the extra salt for a period of a few days caused the systolic pressure to rise from an average level of 110 mm of mercury to 175 mm and the diastolic from 80 to 115. At the same time the urinary glucose excretion fell from between 60 and 70 grams to between 10 and 20 grams daily. Apparently this result was dependent in part upon the diets being relatively low in potassium.

That these phenomena were not peculiar to the patient who suffered from an abnormal craving for salt was shown by the fact that two other diabetic children

showed similar though less marked reactions under the same conditions except for somewhat lower salt intake. In one experiment in which KCl was substituted for NaCl the blood pressure was lowered while the degree of glycosuria was increased.

Several phases of the problem are being further investigated.

Hypoplasia of Enamel of Teeth (Familial) Lawrence F. Richdorf M.D., Minneapolis, Minn.

Cockayne has described hypoplasia of the enamel of the teeth, or agenesis of the enamel. The condition affects both the teeth of the first and second dentition. The teeth are often brown when erupted and are not as resistant as teeth with normal enamel. In every instance affected members pass on the anomaly to the next generation. Not all are affected the proportion in the known cases reported and summarized by Cockayne being 86 affected to 51 not affected. The number of males to females affected were 47 to 48, respectively the proportion of normal males to females 24 to 23. The defect is a dominant, with no limitation to sex and with a greater occurrence of the abnormal.

The family to be reported is of interest because of the extensive enamel lesions and the recurrence of the same for five generations. Two other families have been found but this is the first time opportunity for study has been afforded.

Factors Responsible for Involuntary Defecation in Children. Hyman S. Lippman, M.D., St. Paul Minn.

There are physical as well as psychologic factors responsible for the child's soiling himself at an age when this should no longer occur.

One case was that of a young child who failed to be trained because of the marked anxiety displayed by the parents that she be trained. When the parents were made to understand that it was their anxiety that was causing the sphincter spasm, their attitude changed and the problem cleared up.

Occasionally a child placed in a boarding home against his wish may soil himself hoping that through this behavior he will become unbearable to the boarding mother and will be returned to his own home. In such instances the habit ceases as soon as the motive is recognized, and the child is helped to accept the situation from which he is trying to escape. It is frequently impossible to determine to what extent the soiling is due to wilful behavior and how much of it is due to factors over which the child has no control. Intensive interviewing may be necessary to establish this point.

We have been able to understand more clearly the part played by anxiety of a subtle nature in the production of involuntary defecation through the contributions of the psychoanalytic school. Analysis of young children has demonstrated that the disgust shown toward the stool is a reaction against a forbidden pleasure that the young child fights to retain the power to decide when and where he shall have a bowel movement and that peculiar character traits are associated with an exaggerated interest in stool.

Congenital Megacolon Treated by Daily Hot Irrigations of Normal Saline at 115 F. Aaron Friedell, M.D., Minneapolis, Minn.

Hot saline irrigations at 115 F are recommended as worthy of further investigations in treating megacolon. Irrigations to be given slowly and overdistention to be avoided. The film shows a method of procedure and the apparatus used to make the daily irrigations simple.

Significance of Hyperventilation in the Tetany Syndrome in the Newborn. W Bay Shannon, M D, St Paul, Minn.

This case is offered as clinical evidence supporting my recent theory that such primary pathologic states as asphyxia, cerebral injury, atelectasis, etc., may give rise to the tetany syndrome through the successive stages of anoxemia, hyperventilation, alkalosis (?), and a lowered ionic calcium. Cyanotic spells, such as occurred four hours after delivery in this case, are interpreted as hyperventilation phenomena and the nervous picture as due in the main to tetany and an accompanying cerebral edema.

Epidural Abscess Emanuel S Lippman, M D, Minneapolis, Minn

Dandy in 1926 first called attention to that epidural spinal abscess in a definite clinical entity. At that time he showed that it could be differentiated from other conditions which had a similar clinical picture, and he especially emphasized the importance of immediate surgery.

According to literature the pathology found was 1 The abscesses are all in the spinal epidural space 2 They are usually found in the thoracic portion of the space

According to Dandy, these infections are due to (1) extension from a neighboring focus of infection, namely, boils or anthrax in the nape of the neck, extra pleural suppuration, osteomyelitis of a rib or of a vertebra, (2) metastatic infection from a distant source, (3) a group with no primary focus (idiopathic), (4) an organism usually the *Staphylococcus aureus*

According to Dandy, there should be little if any difficulty in arriving at a diagnosis of an epidural abscess when the signs of spinal cord compression accompanied by fever and leucocytosis develop and the level of the spinal cord involvement is contiguous with a preexisting infection. If there has been no such previous infection, diagnosis should be made by the following symptoms

(1) A terrific, almost unbearable and unrelenting pain in the back, or along the course of the spinal nerves or in the legs, (2) a latent period of from four to nine days between the time of onset of the excruciating pain, and the motor, sensory, and sphincter paralysis. In every instance paraplegia, as well as sensory and sphincter loss, have either been sudden or have become complete within forty eight hours after its onset. In nearly all the cases reported, there has been a sharply defined bilateral loss of sensation which may ascend depending upon whether or not the epidural abscess has extended upward or has remained localized. In addition to this characteristic story, there is always high fever, tachycardia, leucocytosis, and usually tenderness and rigidity over the spine. The spinal fluid shows a somewhat increased cell count, usually of polymorphonuclears, and a complete block always exists in the spinal canal, hence low pressure.

The sudden onset of paraplegia usually leads to the diagnosis of myelitis or even thrombosis or embolism. These conditions may be eliminated (1) because of presence of the excruciating pain which for several days precedes the paralysis, (2) because of the tenderness and rigidity of the spine, and (3) by a demonstration of a spinal subarachnoid block.

Although meningitis might be diagnosed because of the rigid neck, positive Kernig sign, fever, and leucocytosis, yet the sensory and motor involvement and the absence of meningitic fluid, plus the presence of a spinal subarachnoid block, should easily exclude meningitis.

Inflammatory epidural tumors may cause similar pain, but they lack the characteristic sharp onset, are less fulminating, and are prolonged over a period of weeks or months instead of days.

Pohomyelitis does not have excruciating pain with localizations in the back, nor would it present a complete arachnoidal block.

The case which I should like to present is that of a thirteen year-old girl admitted to the Minneapolis General Hospital, Dec. 10, 1933 complaining of urinary retention for thirty-six hours, severe excruciating pain in the back for ten days, and paralysis of the lower extremities one day.

The pain in the back just above the waistline at first was rather mild and was helped by hot water bottles, but during the last six days it had been very severe and no treatment relieved it. There had been some weakness of the lower extremities during the preceding four days with progressive difficulty in walking, the legs becoming numb, and in the preceding twenty four hours, a complete paralysis of the lower extremities had obtained.

There was nothing in her past history or family history which had any bearing on the present condition.

On admission the patient weighed 86 pounds and the temperature was 100.8 F. There was a complete motor and sensory paralysis below the thoracic vertebrae, mild neck rigidity, negative Brudzinski sign, absent knee jerks, positive plantar reflexes, and absent abdominal reflexes. The patient was quite alert mentally but complained continually of pain in the back.

Patient was catheterized and yielded a negative urine. blood count was 14,000 polymorphonuclears, otherwise negative. X-ray examination of chest and the thoracic and lumbar spines revealed no pathology. Diagnosis on admission was reserved. Spinal puncture a day after admission revealed pressure of 140 mm. clear fluid, cell count of 66 of which 50 per cent were polymorphonuclear leucocytes.

On the second day the level of anesthesia had risen to the nipple line. This line was sharply demarcated posteriorly at the fifth dorsal nerve on the right side, and on the fourth dorsal nerve on the left. There was moderate hyperesthesia above these levels.

Spinal puncture on the third day revealed the same as the previous one. Patient began to complain of weakness of arms, held them rigid, and toward evening had complete paralysis of upper extremities. Throughout this period in the hospital the patient complained continuously of the severe pain in back.

On the fourth hospital day a laminectomy was done. Our preoperative diagnosis was spinal cord abscess. The spines of the third to fifth vertebrae were removed. At the level of the fourth much thick grayish green pus oozed out into the wound from the epidural space. Drains were inserted, patient returned to bed but died several hours later.

Autopsy was entirely negative excepting for findings at site of operation, which showed a large abscess extending from the third to the fifth thoracic segment with softening of the cord to almost liquefaction.

I have presented this case especially to emphasize the fact that because of failure of recognition, we delayed treatment of a condition which is almost as much an emergency as an intussusception.

Pediatric Aspects of the Cleft Palate Problem. Alexander Stewart, M.D., St. Paul, Minn.

The pediatric care of 231 children who have had over 500 operations for congenital clefts of lip and palate at the Children's Hospital of St. Paul is reported. In this group there were no deaths.

The cleft lips were repaired as soon as possible, most of them in the second month. Different complicated rubber dams and other apparatus designed for the feeding in cleft palate cases had been tried but were discarded for the Breck feeder which was found to be the most satisfactory method for mothers and nurses

The feedings were of breast milk if possible. If a formula was used, it was more concentrated than in the case with the normal child. The greatest difficulty was the amount of air swallowed with the food, this problem required a lot of time and patience on the part of the mother.

A child was considered fit for operation (1) when the gain was satisfactory, (2) when temperature was normal for twenty four hours, (3) when there was no nasal infection, (4) when hemoglobin was about 70, (5) when leucocyte count and bleeding and coagulation time were within normal limits.

No routine x ray picture of the thymus was made unless there were symptoms which indicated an enlarged thymus. Food was given to babies with cleft lips until six hours before operation. No sedatives given in cases of cleft lip. The cleft palates were repaired when the babies were fourteen months to two years old.

For the last two years we have been repairing the palate in two stages, first the hard palate and in about three months the soft palate. This has eliminated most of the severe reactions and rhinitis with pulling out of the sutures we formerly had when the repair was done in one operation.

Generally we do not give any preoperative sedative, but in the older children we have been trying moderate doses of sodium amytal. This seems to allay their fears and anxiety and keeps them quieter after operation.

Patients with cleft lips are given sterile water as soon as they can swallow and regular feedings in twenty four hours. The cleft palate patients are given sterile fluids in eight hours, the food is sterile until the sutures are removed.

We found the Breck feeder with a rubber tubing attached more satisfactory than the dropper.

The building up of patients who are poor surgical risks and the postoperative care is a tedious and exacting type of nursing. The results depend probably as much on the nursing as it does on the surgeon.

Morquio's Disease George K. Hagaman, M.D., St. Paul, Minn.

In the last few years there has been reported a growing number of cases of widespread osseous deformities, evidently produced by some interference with the transformation of cartilage into bone, as in chondrodystrophy, but not confined to the long bones and lacking the symmetry of that condition.

The case report of a child with the x ray findings, especially in the upper extremity and in the spine, as well as in the acetabula, is similar to those described in the reports of Morquio's disease.

Undescended Scapula (Sprengel's Deformity)—Congenital Elevation of the Scapula J. Martin Sansby, M.D., and Leo G. Rigler, M.D., Minneapolis, Minn.

Two cases of deformity of the scapula and cervical region were presented, one in a child aged six years and the other in a child of eighteen months. In the first case the deformity, which is bilateral, was recognized when the child was ten days old. The other, first seen at six months of age, presents a right sided deformity.

That the term "congenital elevation of the scapula" is not the proper designation for this deformity is evident when one considers the embryology of the scapula. In the light of our present knowledge, this condition should be known as "un-

descended scapula.' It is often associated with other congenital deformities, such as defective ribs, numerical variations of the vertebrae and spinal and muscular defect.

For practical purposes this deformity may be divided into three types (1) in which there is a defect in the cervical spine—usually spina bifida (an omovertebral bone may or may not be present) (2) in which there are muscle defects (3) in which there is a bony bridge connecting the scapula to the spine with no spinal defects. In all the above types as a result of the molding effects of the muscles, there is a forward bending of the supraspinous portion of the scapula.

Treatment varies with the character of the case. In cases in which the deformity is slight and the descent is not prevented by fibrous and bony attachments, gymnastics, passive motion and stretching are all the treatment required. In cases in which the elevation is pronounced with marked deformity and in which articulations and adhesions are present surgery is indicated. In all cases the after treatment should be active exercise, passive motion, and massage.

The Cardio-Amplifier and Sound Tracings in the Diagnosis of Cardiac Murmurs.

Paul F. Dwan, M.D., Minneapolis, Minn.

Four cases are presented with demonstration on the cardio-amplifier and accompanying sound tracings. The first is a normal heart the next two are cases of mitral regurgitation and the last a case of patent ductus arteriosus. The mitral cases showed the differences in tracing between a soft systolic murmur and a loud harsh murmur. The last showed the harsh, prolonged, machinery like murmur of patent ductus arteriosus.

Primary Sarcoma of the Suprarenal With Metastasis to the Skull. Charles L. Steinberg, M.D. St. Paul, Minn.

This syndrome, which is sometimes termed 'Hutchinson's sarcoma,' occurs in infancy and early childhood. Clinically it presents a picture so strikingly bizarre and grotesque that once seen it can hardly be forgotten.

The primary lesion is in the suprarenal gland but the earliest clinical sign commonly observed is an ecchymosis of one or both of the eyelids. Within a very few days exophthalmus develops this is usually unilateral. As this exophthalmus increases, a tumor mass or masses in the adjacent temporal and frontal bones appear followed rapidly by metastatic enlargement of the preauricular and cervical lymph nodes. In some cases exophthalmus of the other eye occurs. Localizations elsewhere in the skull usually appear sometimes metastatic growths in the ribs, vertebrae and long bones are found. Peculiarly the primary growth in the adrenal was found clinically in only about half the reported cases, and in these usually after the skull changes were manifest.

The metastatic tumor masses increase rapidly in size and number, at first they are rather firm and solid in nature but commonly central softening of the masses occurs, producing a rubberlike consistency. These deforming tumor localizations in the skull produce a striking similarity of appearance of all of these patients.

A rapid spread of the malignancy is associated with a profound secondary anemia and progressive exhaustion. The leucocytic blood picture shows no definite changes. The entire progress of the disease is extremely rapid, death occurs in from one to six months after the initial ecchymosis is observed.

The postmortem findings are rather constant. The primary adrenal tumor varies from the size of a walnut to that of a coconut. It is usually unilateral. The adjacent kidney may be involved by extension, but the other abdominal viscera are

The cleft lips were repaired as soon as possible, most of them in the second month. Different complicated rubber dams and other apparatus designed for the feeding in cleft palate cases had been tried but were discarded for the Breck feeder which was found to be the most satisfactory method for mothers and nurses

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The onset may be sudden or insidious, often after an acid meal. In the acute state the gland is hot painful and tender. There is slight fever. Aropy discharge, sometimes offensive in taste may be expressed from the duct. Attacks last one to three weeks.

The cause may be (1) local as dental caries, tonsillitis, sinusitis, or stomatitis (2) subsequent to an acute suppurative parotitis that has drained externally (3) stones; (4) stenosis of duct, (5) tuberculosis, syphilis, or actinomycosis.

The involvement may be lobar, lobular or diffuse.

The treatment consists of the following procedures: (1) massage of the parotid every morning before breakfast (2) frequent gum chewing to stimulate the flow of saliva, (3) a glass of sour lemonade after meals (4) treatment of local disturbances, as infected tonsils, sinusitis or stomatitis (5) improvement of general health and immunity by high vitamin diet and perhaps vaccine; (6) the use of lipiodol as a diagnostic and perhaps therapeutic aid. Its therapeutic action may be (a) similar to that of bismuth paste in the healing of chronic cavities or sinuses (b) as an aid to drainage by dilating the finer ducts, and (c) its possible antiseptic action as suggested by some in pulmonary bronchiectasis and (7) surgery, as removal of calculi or dilatation of ducts.

Prolonged Fever Following Encephalitis. Thomas Myers, M.D., St. Paul, Minn.

A female infant was presented with a complaint of almost constant fever following acute encephalitis ten months before. The condition is considered one of 'cerebral' or 'neurogenic' fever due to a disturbance of the thermoregulatory center in the optic thalamus, resulting from acute encephalitis ten months previous.

The Liabilities Versus the Assets Originating From Primary Tuberculous Infections. C. A. Stewart, M.D. Minneapolis, Minn.

Wallgren has shown tuberculous meningitis to be an immediate hazard created by the first invasion of the body with the tubercle bacillus, and personal experiences combined with circumstances relating to the age at the time of death, identify military tuberculosis as a second immediate hazard attending primary tuberculous infections. The number of children who die annually with these two conditions following shortly after the first infection is laid down represents a heavy sacrifice paid for an alleged immunity.

The records of 11400 children examined at Lymanhurst during the past twelve years identify phthisis as a remote liability created by the first infection with *Mycobacterium tuberculosis*. This statement is based on the fact that during this follow up period more examples of this form of tuberculosis have arisen in the patients who entered Lymanhurst with positive tuberculin tests than in the group who were negative to tuberculin when first examined. The liabilities attending the initial invasion of the body with the tubercle bacillus include military tuberculosis, tuberculous meningitis and phthisis.

To date the Lymanhurst studies have disclosed no assets which can be attributed to the acquisition of tuberculosis of the first infection type. Apparently, therefore the rather generally accepted belief that the first infection with the tubercle bacillus produces a beneficial protective immunity must be abandoned.

Natural Hypersensitiveness in Children. Albert V. Stoesser, M.D., St. Paul, Minn.

From 2771 admissions to the General Pediatric Out Patient service of the University of Minnesota Hospitals over a two year period 141 children, or 5 per cent, were referred for study and treatment to the pediatric allergic clinic. The cases

were distributed as follows eczema, 43 (30.5 per cent), allergic coryza, 10 (7.1 per cent), hay fever, 19 (13.5 per cent), asthmatic bronchitis, 5 (3.5 per cent), bronchial asthma, 46 (32.6 per cent), urticaria, 15 (10.7 per cent), and gastro intestinal allergy, 3 (2.1 per cent). All of these cases can be classed under that subheading of allergy called "natural" or "human hypersensitiveness," which includes all clinical forms of allergy which occur so far as is known only in human beings and which are subject almost entirely to inheritance.

A Study of the Mortality of Premature Infants Delivered by Cesarean Section. **Edwin F. Robb, M.D., Minneapolis, Minn.**

A study of the mortality for premature infants delivered at the University of Minnesota Hospital and at Abbott Hospital for the past five years revealed a 41 per cent mortality for premature infants delivered by cesarean section and a 34 per cent mortality for premature infants delivered by vaginal methods.

The theory is suggested that a lowered blood volume may play a large part in causing the high mortality for prematures delivered by the present technic of cesarean section. With the present technic, whereby the cord is cut immediately upon opening the uterus, it would seem that a substantial amount of fetal blood in the placenta was lost to the baby. While the placenta is smaller in the case of a premature infant and no doubt contains less than 90 cc of blood, the percentage of blood lost in this way is high when considered against the small total volume normally present. It may in some cases represent as much as 33 per cent of the total blood volume. Any such percentage loss could account for many of the unexplained cyanotic attacks and fatalities that occur during the first forty-eight hours of life.

R. T. LaVake suggests that the present technic of cesarean section could possibly be modified, delivering the baby, cord, and placenta intact. If this were done, ample time could be allowed in clamping the cord. By thoracic aspiration on the baby's part and by mechanical pressure upon the placenta, much of the fetal blood present in the placenta might be obtained by the baby.

Furthermore, this same theory may apply to premature infants delivered by vaginal methods if the cord is cut before pulsation ceases. Delivery rooms should be supplied with suitable heat lamps and warm cotton gowns to protect the premature baby until all pulsation of the cord has ceased.

The Conservative Treatment of Late Cases of Acute Appendicitis. Owen H. Wangenstein, M.D., Minneapolis, Minn.

If every patient with acute suppurative appendicitis were operated upon early, there would be no necessity for this discussion. Procrastination, purgation, and perforation are the alliterative sequence synonymous with peritonitis and peril of the patient with acute appendicitis. The time interval following the acute attack, after which the nonoperative plan is to be preferred to operation is difficult to establish arbitrarily. It is the status of the patient rather than the time interval that is significant. If it is believed on the basis of the patient's reaction, viz, the pulse and temperature and the local physical findings, that the appendix is ruptured, it is wise to follow the conservative plan of treatment.

Speech Defects in Children. Bryng Bryngelson, Ph.D., Minneapolis, Minn.

The usual classification of disorders of speech is defective voice, articulatory deficiency, aphasia, and stuttering.

We think of good speech in children as being indicative of growth or maturation. Likewise inadequate speech is often indicative of a retarded growth of the nervous

mechanism responsible for speech. Disorders of voice and articulation can be caused by various obstructions in the peripheral speech mechanism. Hypertrophied tonsils and adenoids, nasal polyps, a too large or a too small tongue malformed dental arches short velum, inadequate frenum deviated septum, and cleft lip and palate are the most common types of obstructions to free and easy articulation.

Many children have deficient hearing mechanisms. Certain frequency bands for specific sound groups may be missing in the child's audition. Defective 'f', 's', 'th', 'v' and 'k' sounds are frequently due to the fact that those sounds have never been registered in the auditory pattern of the child even though they have been in the child's speech environment.

At present there are two main approaches to the problem of stuttering. Dr Kopp at the University of Wisconsin is making a biochemical approach to stuttering. His metabolic studies have revealed that the blood pattern as shown by the correlations of total serum calcium inorganic phosphate, total protein, and nonprotein nitrogen is practically the reverse of the pattern of nonstutterers. Some day it may be possible to assist stuttering therapy with certain diets.

At our own university we have been engaged in the approach known as cerebral dominance for the past eight years. By cerebral dominance we mean that in the act of speaking one cerebral hemisphere because of its greater strength, superimposes on the other hemisphere its inherent rhythm pattern, and intensity. Thus when the nerve impulses arrive on the bilateral midline speech structures they do so simultaneously with similar pattern and intensity. Speech, then, becomes a concerted act sponsored by a very high type of integration of the central nervous system. In stuttering the power becomes equalized in both hemispheres, thus causing a reduction of cortical control over the substructures. A stutterer it is indicated from Dr Travis' experimental action current studies, does not possess a sufficiently strong gradient for speech resident in one cerebral hemisphere.

In normal speakers, the dominant speech gradient is resident in the hemisphere contralateral to the preferred hand. Dr Weisenberg's study on aphasia verified this fact when he made an analysis of ninety-eight cases of unilateral cerebral lesion. He found that the dominance as shown by handedness is a good criterion of the hemisphere for speech in approximately 95 per cent of the cases. This does not appear to be quite as true with stutterers because from 75 to 90 per cent have been shifted in handedness. We have found that they come from a left handed stock. In seven hundred clinical stutterers, 83 per cent of them had a history of left handedness in the family.

Pediatricians can well afford to warn parents not to meddle with the native handedness of children. Left handedness is a perfectly normal expression in about thirty out of every one hundred children born. It is our present belief that this transfer deranges inherited neural patterns for speech, writing and reading.

Academy News

The annual meeting of Region IV of the Academy will be held in Seattle on August 9 and 10 1935. This meeting will take the place of the fall meeting of the North Pacific Pediatric Society.

Dr J. Lewis Blanton of Fairmont has accepted the chairmanship for West Virginia.

Comments

THE Fifth Annual meeting of the Academy, which will be held at the Waldorf Astoria Hotel in New York on June 7 and 8, promises to bring together the largest group of pediatricians which has ever assembled in the United States. Although at the time this is written the meeting is two months off, approximately 250 members have already registered for the Round Table Discussions. According to an estimate based on previous meetings, the attendance should reach to between four and five hundred. The final program will reach the members before this comment. The Panel Discussions have been increased as a result of the way they were received and liked at the meeting last year.

One important arrangement that has been made for the first time is the reduced railroad fare on the "certificate plan." Members should buy a one way ticket to New York and obtain at the same time a "convention certificate." This, when validated at the meeting, entitles the holder to purchase a one way return ticket at one third the regular fare. Whether one plans to use the certificate or not, he should obtain it with his one way fare and have it validated, as convention rates require a certain number of certificates to obtain the reduction.

The commercial exhibit will be larger than in previous years. We urge the members to take the time to go carefully and thoroughly through the exhibit. It helps defray the expenses of the meeting and will be successful only to the extent to which the members show an interest.

Exhibitors

Scientific

	BOOTH		BOOTH
American Child Health Assn		H. J. Heinz Company	1
New York City	22	The Larsen Company	D
Children's Bureau		Libby, McNeill and Libby	4
Washington, D. C.	24	J. B. Lippincott Company	6
Children's Welfare Federation		Mead Johnson & Company	B and C
of New York City, Inc.	23	Medical Case History Bureau	16
Department of Health		Mellin's Food Company	11 and 12
New York City	25	Merek & Co., Inc.	E

Commercial

Arch Corrector Corporation	3	The C. V. Mosby Company	15
Cameron's Surgical Specialty Co.	7	M. & R. Dietetic Laboratories, Inc.	F
Harold H. Clapp, Inc.	19	Ralston Purina Company	9
R. B. Davis Company	17	Scientific Sugars Company	8
The Dry Milk Co., Inc.	13 and 14	S. M. A. Corporation	20
Food Concentrates, Inc.	2	Steri Seal Corporation	21
Gerber Products Company	A	Stokely Brothers & Company	10
Health Products Corporation	18	Tailby Nason Company	5

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Original Communications

WHOOPIING COUGH

II EXPERIMENTAL STUDY

CHARLES S. CULOTTA, M.D. DANIEL F. HARVEY, M.D., AND
ERNEST F. GORDON, M.D.
NEW HAVEN, CONN.

THE rôle that the bacillus of Bordet and Gengou plays in the etiology of whooping cough is still disputed. Current opinion seems to be divided between those who favor the pertussis bacillus as the sole specific cause and others who believe that a filtrable virus acts at least as a necessary predisposing agent. Investigations on both aspects of the problem are being presented in this paper.

PART I

The mass of evidence at hand shows that the Bordet-Gengou organism bears an important relationship to the disease. First, the presence of *H. pertussis* in a relatively high percentage of whooping cough patients early in the disease has been definitely established by many observers by the use of the conch plate method for early diagnosis (Chievitz and Meyer,¹ Lawson and Mueller,² Sauer and Hambrecht,³ Gardner and Leslie,⁴ Culotta and Harvey,⁵ and others). The gradual disappearance of the Bordet-Gengou bacillus goes hand in hand with the decline in infectivity. Second, the organism is distinct from other species of bacteria and is absent in other catarrhal infections. Third, the appearance of complement fixing bodies for *H. pertussis* during convalescence from whooping cough has been demonstrated. Fourth, *H. pertussis* has been recovered from the lungs of children who died of pneumonia complicating whooping cough (Smith,⁶ also Fontayne⁷). Fifth, the results of experimental infection, although contradictory, merit serious consideration. The early claims to the suc-

successful implantation of *H. pertussis* in laboratory animals are open to serious criticism since methods were not available at that time for differentiating the pertussis bacillus from the distemper bacillus (This is undoubtedly the basis for the contradictory reports in experimental whooping cough investigations) More recent claims to the experimental transmission of the disease to animals are highly suggestive Sauer and Hambrecht⁸ reported the production of a characteristic paroxysmal cough in eight out of twenty-eight monkeys (a total of seventy-six tests) inoculated with *H. pertussis* The cough was accompanied by a moderate lymphocytosis, and *H. pertussis* was recovered from deep throat cultures These animals were found to be refractory to subsequent inoculations of *H. pertussis*, but unfortunately no mention is made of controls More recently, Rich, Long, Brown, Bliss, and Holt⁹ reported the production of a pertussis-like affection in a chimpanzee following inoculation with unfiltered sputum from a human case of pertussis and in two other chimpanzees following inoculation with suspensions of freshly isolated Bordet Gengou bacilli Mild catarrhal affections simulating colds were also observed in the two apes inoculated with unfiltered sputum These authors state that "there can be no doubt that the three apes inoculated with pure cultures of Bordet bacilli or whole sputum developed typical whooping cough, which in its clinical and bacteriologic aspects was indistinguishable from the human disease" Shibley¹⁰ has also reported transmission of whooping cough to apes following inoculation with *H. pertussis* MacDonald and MacDonald¹¹ have reported the transmission of whooping cough to two children by intranasal instillation of *H. pertussis*

It is apparent from the preceding considerations that legitimate claims to the successful experimental implantation of the *H. pertussis* are not very numerous, it is desirable to know more about the infectivity of laboratory animals to the organism in question Therefore, we are reporting the results of our investigations in this field

METHODS

The procedure used in the preliminary experiments consisted in the intratracheal inoculation of monkeys with saline suspensions of *H. pertussis* Only strains recently isolated from cases of whooping cough were used (first to third generation cultures isolated from a cough plate) The culture medium used was essentially the Danish modification of the original Bordet Gengou medium as recommended by Gardner and Leslie,¹² but human citrated blood (20 per cent) was substituted for horse blood From forty eight to seventy two hour surface growths on three 15 cm. Petri dishes were suspended in 10 c.c. of physiologic sodium chloride solution, and from 2 to 4 c.c. of the suspension was injected in the monkeys. The virulence of the organism for white mice was determined by intraperitoneal inoculation, from 0.2 to 0.5 c.c. of this suspension being in all strains used the lethal dose (Sauer and Hambrecht's) The organism was readily recovered from the peritoneal cavity and heart's blood All fresh strains were agglutinated by Gardner and Leslie's¹² Phase I antiserum in dilutions ranging from $\frac{1}{4000}$ to $\frac{1}{2000}$

The monkeys used in the early experiments were of the *Erythrocebus* variety or the so-called "military" monkey. The *Macacus rhesus* was used subsequently because the monkeys of the former species were not available. The animals were under preliminary observation for a period of a week to two months. Frequent deep nose cultures were obtained to determine the normal bacterial flora. Distemper bacilli were not observed in these animals. Daily temperature readings and white blood count were taken, and the animals were weighed at intervals. The intratracheal route was used with the monkey strapped on the operating board and head fully extended. An anesthetic usually was not necessary, but it is probably desirable.

EXPERIMENTAL

1. *Intratracheal Injection of H. Pertussis*—The intratracheal route of infection was chosen because a heavy inoculation of the respiratory tract can be effected in

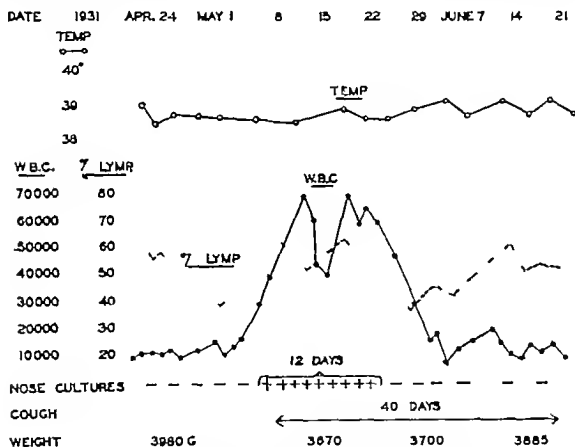


Chart 1—Experiment 1. Experimental pertussis.

this manner. Three monkeys, two of the *Erythrocebus* variety and one *Macacus rhesus* developed a pertussis-like syndrome as is shown in the following protocols.

EXPERIMENT 1. (Chart 1.) Monkey Δ *Erythrocebus*, female weighing 3,080 gm., May 1 1931 was given an intratracheal injection of 4 c.c. of a saline suspension of virulent *H. pertussis* (Lawrence strain) which was prepared by washing off one plate of a seventy-two-hour culture (on Bordet-Gengou medium) in 10 c.c. of saline. The monkey remained well until May 8 the eighth day, when a cough developed and the leucocyte count began to rise with a corresponding increase in the lymphocytes. Deep nasal cultures remained negative for *H. pertussis* from the time of inoculation until May 8 just before the onset of the cough. Cultures were positive for twelve days, this period being not unlike the catarrhal stage clinically. The cough became more spasmodic and vomiting occasionally occurred. The total duration of the cough was forty days. The white blood count reached its maximum at the

height of the cough, the highest reading being above 70,000 per cubic millimeter, the average count prior to inoculation was 15,000 per cubic millimeter. Signs of a diffuse bronchitis (rales, both bases posteriorly) were noted during this period. A roentgenogram of the chest showed an area of increased density in the left lower lobe. The lymphocytic response did not exceed 60 per cent, the base line during the preliminary period of observation being approximately 45 per cent. The temperature curve remained within normal limits. The animal lost weight but regained it during convalescence. This monkey has been under observation for a period of two years and has been well. No cough followed two subsequent similar attempts at reinfection to test immunity, but no conclusions as to immunity can be drawn since the control animals (*Macacus rhesus*) were also refractory.

EXPERIMENT 2 (Chart 2) Monkey 2, *Erythrocebus*, male, weighing 3,020 gm, May 1, 1931, was given an intratracheal injection of 4 c.c. of the same saline sus

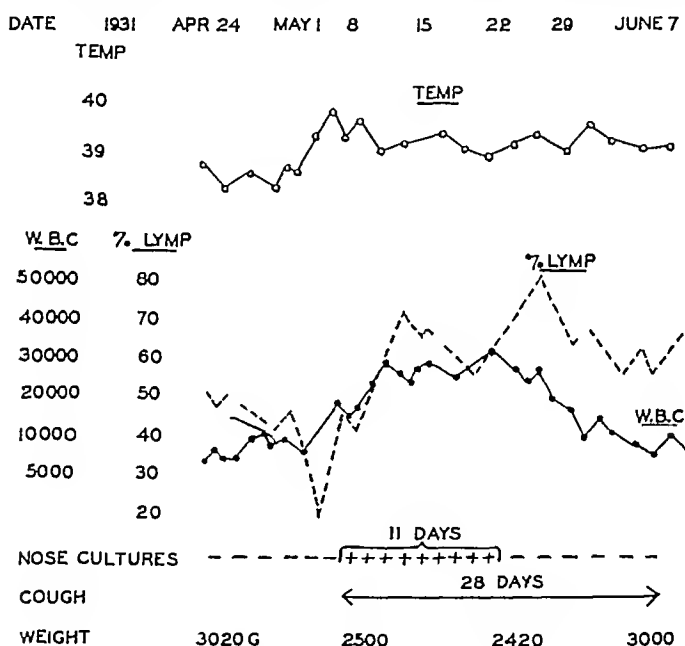


Chart 2—Experiment 2 Experimental pertussis

pension of Lawrence strain as in Experiment 1. Daily deep nose cultures were negative for *H. pertussis* until ninth day when organism was recovered. The nose cultures were positive for eleven consecutive days. The cough began on the tenth day, May 10, and coincidentally there was a gradual rise in the white count with a definite lymphocytic response. The cough became progressively worse and more frequent, from three to four attacks occurring at times within one half hour. The total duration of the cough was twenty-eight days. The white count reached its peak on the twentieth day, being 32,000 per centimeter, the average count prior to inoculation having been 8,000 per cubic millimeter. The lymphocytic response exceeded 75 per cent. There was only slight febrile reaction during the course. A loss of weight occurred as in Monkey 5, but a gradual gain occurred during convalescence. This animal remained well for a period of five months after this experiment and then developed a spontaneous, Group IV, pneumococcus pneumonia with meningitis. There were no signs of tuberculosis noted at postmortem examination.

EXPERIMENT 3 (Chart 3.) Monkey 77 *Macacus rhesus* female weighing 3,550 gm., March 28, 1932, was given an intratracheal injection of 5 c.c. of a saline suspension of virulent *H. pertussis* four different strains being used. The suspension was prepared as in Experiment 1. The monkey began to cough on the eighth day and continued to cough for thirty six days. The deep nose cultures were positive for *H. pertussis* for a period of twelve days. The white count gradually rose to above 50,000 per cubic millimeter the base line prior to inoculation being 20,000 white blood cells per cubic millimeter. The lymphocytic response in this animal was not as striking as in the previous experiments. The lymphocytes averaged 50 per cent prior to inoculation and at the height of the cough reached 60 per cent. The early loss of weight was again noted. This animal continued well for three months, then succumbed to an ulcerative enteritis. Autopsy revealed no signs of tuberculosis.

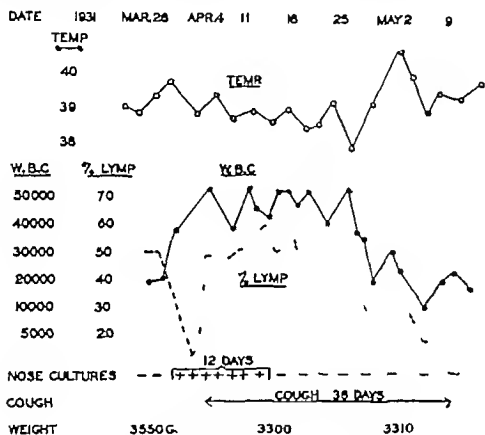


Chart 3 — Experiment 3 Experimental pertussis.

DISCUSSION

The results of the foregoing experiments may be summarized as follows

After intratracheal inoculation of virulent *H. pertussis* two *Erythrocebus* monkeys and one *Macacus rhesus* monkey developed a syndrome which closely resembles the disease as seen in man. First, the incubation period varying from seven to ten days observed in these experiments is the generally accepted incubation period of the natural disease. The second comparable feature is the ease of recovery of the organisms early in the illness, the period described in human cases as the 'catarrhal phase'. It has been definitely established by many observers that it is during this early phase of whooping cough when *H. pertussis* can be readily isolated by the cough plate method in a relatively high percent

lent *H pertussis* organisms. The criteria for infection presented were (1) incubation period of seven to ten days, (2) recovery of organism early in the illness, (3) leucocytosis with a predominance of lymphocytes, (4) cough which became spasmodic, lasting twenty eight to forty days with subsequent recovery.

2 Inoculation in *Macacus rhesus* monkeys with filtered and unfiltered nasal washings from cases of whooping cough gave negative results. Combinations of filtered washings and organisms also proved negative.

3 Measles virus did not favor implantation of *H pertussis* in *Macacus rhesus* monkeys.

CONCLUSIONS

1 Experimental results which add further support to the bacillus of Bordet and Gengou as the specific agent in whooping cough are presented.

2 The monkey is probably not the ideal animal for experimental whooping cough investigation.

The authors express their grateful appreciation to Dr James D Trask for his assistance in this study.

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ENTERITIS IN INFANTS PREVENTION OF ITS SPREAD

DICK DIET KITCHEN AND ASEPTIC NURSERY TECHNIC

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EVANSTON, ILL.

TO NURSE at the breast was through the ages the only protection against infantile enteritis. At the close of the nineteenth century Budin,¹ the Paris obstetrician, made the clinical observation "In sterile milk alone is safety, and it must be made the basis of all artificial feeding." Chapin² in 1915 found a high infant death rate persisting in institutions. In the state of New York in eleven asylums for infants it ranged between 18.3 and 57.6 per cent with an average of 42.3 per cent. In ten institutions in various American cities it varied between 31.7 and 75 per cent! For infants of the same class in boarding homes he reported a mortality of but 12 per cent. Through concerted efforts, such as the infant welfare movement, the purification of drinking water, the pasteurization and boiling of milk and prophylactic pediatrics the "summer peak" of infant deaths gradually disappeared. Were it not for reliable epidemiologic data it might seem that modern infant feeding had completely triumphed over infantile enteritis. The League of Nations' report on enteritis³ shows that it persists as a leading cause of infant deaths in all countries and large cities. In the United States birth registration area (26 states) enteritis caused 17,291 infant deaths in 1930, 14,021 in 1931 and 10,791 in 1932.

This disease highly contagious for young bottle fed infants, wreaks havoc wherever it gains access. Its communicability is seldom sufficiently stressed. Newborn infants, who spend less than the first fortnight in modern maternity nurseries are relatively safe. That this security rests more on the absence of the causative microorganism than on the nursery technic is evinced by the periodic outbreaks of this bane of the neonatal nursery. Infants at home on the breast, or on supervised boiled feedings are likewise more protected by their isolation than by the household technic. The outpatient infants with enteritis prove that their protection is only relative. Although the carnage of a former day no longer exists, institutions housing artificially fed infants from diverse sources still show a comparatively high incidence of enteritis. This prevalence is in no small measure due to secondary cases. Not the absence of enteritis, but its presence without a secondary case over long periods of time is the ultimate test of a precautionary technic. To prevent the spread of enteritis and other infections many hospitals, infant asylums, orphanages day

nurseries, and boarding homes have instituted sterilized food, cubicles, and special nursery rules

When The Cradle opened in 1923 for the care of homeless infants until their adoption,* the diet kitchen and nursery technic of a leading infant hospital were expected to meet any emergency. The infant, on admission, was placed in an isolated, cubicled crib with "special precautions" technic for a fortnight and admitted to the general nursery if well at the end of that time. Morbidity and mortality remained low for years. With twenty deaths in four years, the mortality rate was 4.8 per cent. Eighteen of these deaths were due to enteritis, eleven of the infants had contracted it in the institution. Scattered over a period of four years, these deaths were charged to "the hazards of institutional care of homeless infants." Because enteritis would often be absent for months at a time, there seemed to be no reason to question the efficacy of the precautionary technic.

Two infants (No. 462 and No. 463), born in Chicago hospitals, were admitted on Feb. 3, 1927. Both developed enteritis, one child died within a few days, the other developed complications, including mastoiditis. Because they typify the two forms of enteritis encountered in the epidemic which followed, excerpts from the clinical, nursing, and postmortem notes follow.

CASE 1—(No. 462) Clifton was born Jan. 17, 1927, weight, 6 pounds 6 ounces. He was admitted, Feb. 3, 1927, when he weighed 6 pounds 10 ounces. Entrance examination was negative. Blood, stool, urine, nose and throat cultures, rectal temperature, etc., were normal.

February 4 to 8. He was apparently well, stools apparently normal. February 9. His weight was 6 pounds 14 ounces, rectal temperature, 100.4° F., he was fretful, had moderate abdominal distention, refused food, and vomited, he passed four semi-liquid stools with curds and mucus, last two containing blood. February 10. Rectal temperature was 103.4° F., abdominal distention increased, pallor increased, he was toxic, had irregular respirations, and died.

Anatomic Diagnosis (Dr. J. Lisle Williams). Acute hemorrhagic enteritis, acute hyperplasia of mesenteric lymph nodes, acute fibrinopurulent peritonitis.

CASE 2—(No. 463) Sybil, was born Feb. 1, 1927, and weighed 6 pounds 10 ounces. She was admitted Feb. 3, 1927, weighing 5 pounds 14 ounces. Entrance examination was negative. Nose and throat cultures, vaginal smears, blood, urine, stool, and rectal temperature were normal.

*Infants unfit for adoption are not admitted or promptly returned to the mother or transferred to a suitable institution. Congenital syphilis is rarely encountered because reputable laboratories perform Wassermann tests on the mother's blood usually before the infants are admitted. Excluded are infants with syphilis, gonorrhea, tuberculosis, gross anomalies, gross congenital defects, birth paralysis, brain injuries, mongolism, cretinism, etc. Insanity, hereditary nervous diseases, chronic alcoholism, etc., in either parent, debar the infant. Early legal adoption of the healthy illegitimate infant, by carefully selected foster parents, eager and able to care for the infant as their own, appears to be a rational solution to this age-old problem. A theory occasionally promulgated by psychologist or social welfare worker that the state legally compel all unwed mothers to keep their offspring for at least a year would force many more girls to risk the hazards of criminal abortion. Many more infants would die from enteritis or other infections of those who might grow up not a few would become a burden to the state. With a declining birth rate, the urgency of saving these infants increases in importance. The Cradle's method is a step forward in social evolution because it is now the safest and most humane plan devised for the unwed mother and her child.

February 4 to 15 she was apparently well there was a slight gain in weight, and the stools were apparently normal. February 16 Weight was 6 pounds 10 ounces rectal temperature 100.4 F she was fretful, had moderate abdominal distention, refused food vomited and was pale. She passed four semiliquid brown stools of foul musty odor. February 17 18 She was rather listless stools as above. February 19 Weight was 5 pounds 10 ounces rectal temperature from 102.8 F to 104 F pulse 140 respirations 44 bilateral myringotomy performed by attending otologist.

February 21 Weight was 5 pounds 4 ounces rectal temperature 103 F abdominal distention increased. She was transferred to the hospital bilateral mastoidectomy was performed and the infant died.

Anatomic Diagnosis (Dr J Lisle Williams) Bilateral, acute suppurative otitis media and mastoiditis acute, generalized fibrinopurulent leptomeningitis and ethmoiditis septic thrombosis of lateral venous sinuses hyperemia of intestinal wall hyperplasia of mesenteric lymph glands submucous hemorrhages of stomach and colon Smears and cultures from ear and mastoid wound streptococci in chains. Spinal fluid culture *B. coli*.

During the following eight months eighty-six infants contracted enteritis. The twenty-seven deaths of 1927 were due to enteritis twenty-one of these infants developed the first symptoms after they had been in the institution longer than ten days (Table I). When the customary attempts at eradication of the infection (complete change of nurses disinfection and painting of the entire nursery etc.) were of no avail Dr Gladys H. Dick, a director and benefactor of The Cradle in collaboration with Dr George F. Dick and Dr J. Lisle Williams¹ undertook a complete bacteriologic investigation. When the lactose litmus-agar plate method of culture was used they recovered the Morgan dysentery bacillus from the intestinal lesions of all infants who died. The Morgan dysentery bacillus isolated was highly pathogenic for rabbits. From 1 to 3 c.c. of the whole, forty-eight hour broth culture injected intravenously killed rabbits in from eight to forty-eight hours. From 3 to 5 c.c. of sterile filtrate from forty-eight hour broth cultures injected intravenously killed rabbits within twenty-four hours. The rabbits which received the sterile filtrate and those which received the whole broth cultures showed hemorrhagic enteritis.²

Because the infection was apparently of intestinal origin all feedings and water were boiled ten minutes bottles and nipples were autoclaved. As some of the infants who contracted enteritis were on powdered protein milk dilutions (which were not boiled to prevent curdling) a bacteriologic examination of the various ingredients of all feedings was undertaken by Dr George F. Dick and Dr Gladys H. Dick.³ Unopened cans of these powdered milk preparations when cultured were found to contain a variety of living bacteria including streptococci.⁴ The epidemic came to an abrupt end in November—soon after only sterilized food was given to all infants.

¹The A. M. A. Committee on Foods has since been instituted to approve and regulate the purity of foods.

TABLE I
THE CRADLE ADMISSIONS AND DEATHS FOR TWELVE YEARS

	(AN APPROVED TECHNIC DURING FIRST SIX YEARS)							(DIOL TECHINIO DURING LAST SIX YEARS)						
	1923	1924	1925	1926	1927	1928	6 yr TOTAL	1929	1930	1931	1932	1933	1934	6 yr TOTAL
Admissions	65	83	130	157	257	250	942	254	320	271	253	272	250	1,620
Deaths	2	6	5	7	27	8	55	5	1	3	4	3	1	17
Enteritis deaths	2	6	5	5	27	8	53	5	0	0	0	1	0	6
Infant enteritis (contracted at Tho Cradle)	2	4	4	1	21	8	40	0	0	0	0	0	0	0
	5.8% mortality rate, first 6 yr							1.0% mortality rate, last 6 yr						
	96.0% of deaths due to enteritis							35.0% of deaths due to enteritis						
	75.0% of fatal enteritis contracted after admission							after admission						
	None contracted							None contracted						

That the spread of enteritis may be due to flaws in nursery technic is verified by what happened soon after the subsidence of the 1927 epidemic. Malcolm (No 680) admitted on Dec 16, 1927, came from an obstetric nursery in Chicago where enteritis was endemic. He was placed in a cribed crib under the customary 'special precautions' technic. The course of his illness was quite like that of Sybil (see above). He died Jan 29 1928. On February 15 Philip (No 699) a thriving infant admitted five weeks previously developed enteritis and died ten days later. In May three infants (Nos 769 792, and 795) developed fatal cases of enteritis weeks after admission.

As only sterilized food had been given to all infants Dr Gladys Dick made a detailed survey of the nursery and feeding technic. Cotton applicators for cleansing nostrils made by the nurses (some of them on relief duty with enteritis cases) were being used promiscuously without sterilization. Nurses who bathed the babies and changed diapers also gave feedings. This and other evidence led to the conclusion that *the causative organisms from the feces of an infected infant on the nurses' hands resist washing and contaminate the nipples supplies and food of other infants*. "To avoid transmission of the infection by the fingers nurses were required to put on a fresh pair of sterile rubber gloves for each feeding of each baby and for giving water. Since precautions were also taken in the diet kitchen and throughout the institution no finger was allowed to come in contact with anything that went into a baby's mouth. Diapers of all infants were put in lysol solution immediately on removal." Since 1928 every thing that entered an infant's mouth or nose was sterilized and was not touched except by aseptically clean hands. In 1929 five of the infants, who had enteritis when admitted from Chicago hospitals, died, but no new case of enteritis occurred at The Cradle. Each year since then, infants have been admitted with enteritis, gonorrhea and acute upper respiratory disease but no secondary case has occurred. In 1933 one of the infants admitted with enteritis recovered after an illness of four months, another died ten days after admission but no new case developed.

The absence of a secondary case in six years during which time 1 620 infants were cared for is unique for institutions of this kind and proves the Dick technic flawless. Without sacrificing safety various minor changes have been made for the saving of time labor and material. Because Dr Dick's various suggestions involve diet kitchen, cribed nursing and medical care and have been incorporated as integral parts of The Cradle technic * a synopsis is appended.

A unit consists of twelve cribed cribs, housed in several small communicating rooms. Each unit has its own nurses and supplies. A graduate nurse and two student nurses do twelve hour day duty. A

* For practical suggestions, thanks are due Miss Dorothy Lopnow, R. N., supervisor

graduate and student nurse do twelve-hour night duty. Only these nurses, resident, and attending physicians have access to a unit.

The graduate nurse on day duty is responsible for her unit. She has sole charge of infants weighing less than 6 pounds (in incubators), sick infants, medication and treatments, she takes all cultures and smears, accompanies the attending pediatrician, consultant, and visiting physician, she supervises the work of student nurses, prepares for the diet-kitchen nurse a list of each infant's twenty-four-hour feedings, records on each infant's chart (from the student nurses' notes) weight, rectal temperature, number and quality of stools, urinations, she records food intake, refused and vomited. To the resident she reports fever, distention, repeated vomiting, diarrhea, discharges, skin lesions.

The student nurse gives feedings, weighs, bathes, and clothes the infants, and changes diapers. Her daily observation sheet for each infant is transcribed into the infant's records by the supervising nurse.

The attending pediatrician puts on a clean gown and mask* before he enters a unit. He scrubs his hands with running water, soap and brush, and soaks them in the "clean" basin of disinfectant solution,† then dries on a clean towel. The undressed infant is examined in the crib, the "clean" supervising nurse hands him a "clean" stethoscope, sterile tongue blade, and ear or nose speculum from a "clean" tray. His hands and the stethoscope bowl are then soaked in the disinfectant solution and dried on a clean towel before he proceeds to the next infant. At the conclusion of a visit the resident's findings and the nurses' records of new infants, sick infants, and those ready for adoption are read, he countersigns the resident's notes, if correct, and signs the chart when the infant is discharged. Two regular visits are made each week. Besides the preliminary examination, a final examination is made of each infant at the end of four weeks—the minimum stay—before an infant is recommended for adoption. Consulting dermatologist, surgeon, otologist, psychologist, etc., observe the above precautions.

The resident physician follows the precautionary technique outlined above. He records the complete physical examination of each infant soon after admission and underscores with red ink findings which deviate from the norm. He examines nose and throat cultures, vaginal and eye smears, urine, blood, and stools in the well-isolated laboratory. He takes blood (for Wassermann test) from the heel of infants over three months of age. He prescribes medication and treatment, when indicated, between the attending physician's visits.

*Masks (two layers of handkerchief linen) are worn by everyone in the nursery; proper a removed mask is replaced by a clean one. Used masks are boiled for ten minutes then washed with soap and water, rinsed and dried.

†One tablespoonful of lysol or klomine to a quart of water.

Visiting physicians, who examine infants for prospective foster parents, do not enter the nursery proper. They put on clean gowns and masks and wash their hands in running water. The naked infant wrapped in a clean sheet is placed on the examining table in the 'showroom' which adjoins each unit. The physicians use only the clean stethoscope and sterile supplies from the clean tray.

Adopting parents never enter the nursery. The infant in clean linen, is placed in a crib in the showroom, where the adopting parents, in gowns and masks are permitted to hold, not to fondle or kiss the infant. When the infant is returned to the cubicle crib the clothing is changed. Visitors never enter the nursery. Those over sixteen years of age are permitted to look at the infants through the glass doors leading to the nursery.

Each room has a linoleum floor (mopped daily with hot suds) good natural and artificial light, electric ventilator, hot water heat, humidifier, kitchen sink hot and cold water (foot pedal faucets) drain board large saucepan (for warming bottles), a large bowl of disinfectant solution (for used bottles and nipples) a basin of disinfectant solution marked 'clean' another marked 'contaminated' scales, and sterile forceps in an open jar of disinfectant solution. All floors are 'contaminated' anything dropped is disinfected or put into the wire hamper. Linen soiled with urine or feces is thrown into the hopper can. The corridor walls, windows, and shelf where the feedings are warmed are 'clean'. Walls are wiped twice weekly with disinfectant solution (as far as can be reached). Sinks are 'contaminated'.

A cubicle contains a standard (white) crib (42 x 22 inches), low chair, a shelved enameled bedside table with attached bath basin (for bed bath) a day's supply of clean linen (sheets, diapers, undershirts, gowns, towels) soap. On the top of the bedside table are arranged sterile glass jars with cotton balls (for cleansing buttocks) sterile jars of applicators and gauze squares, 8 oz. bottle of saturated solution of boric acid (for routine cleansing of buttocks) sterile mineral oil, sterile vaseline and rectal thermometer in vial of disinfectant solution. A properly folded gown (for student nurse) hangs on a hook in the cubicle. An open paper bag is pinned to the table for waste cotton, etc. To permit ventilation, the glass partitions are only five feet high.

Within a cubicle an individual aseptic technic is used. Everything is 'clean' for that infant but 'contaminated' for the other infants. Twice a week the cubicle walls and everything in the cubicle is wiped with a cloth saturated with disinfectant solution. The infant remains in the assigned cubicle until ready for adoption. Transfers are never permitted. After the infant's discharge the bed and table are stripped, cubicle walls, crib, table and chair are wiped with cloth saturated with disinfectant solution, crib and mattress are aired out-of-doors for twenty-four hours, the mattress is whisked with disinfectant solution.

The next day the bed is made up with clean linen, the bedside table equipped with sterile supplies and clean linen

At the feeding hour a bottle from each infant's bottle rack in the refrigerator is brought to the nursery in a bottle rack, which is placed in the deep saucepan of hot water. After the supervising nurse of the unit scrubs, disinfects, and dries her hands, she puts on sterile rubber gloves, removes bottle caps, puts on sterile nipples, and covers each nipple with a sterile, creased (four-ply) gauze square (4×4 inches). The student nurse scrubs, puts on a cubicle gown, the diaper* is changed if soiled, her hands are then scrubbed with soap, sterile brush, and running water, then soaked in the "contaminated" basin of disinfectant solution, then in the "clean" basin of disinfectant solution, she dries them on clean towel. She then sits on the cubicle chair with the infant in her left arm, carefully removes the gauze without touching the nipple, and inserts the nipple into the infant's mouth without touching the upper part of the bottle. If nipple needs changing, the "clean" supervising nurse makes the change, if bottle gets cold, the student nurse warms it under the hot tap. Food not consumed is poured into the sink drain, the empty bottle and nipple are promptly submerged in the large pan of disinfectant solution. The student nurse then scrubs, unties gown, scrubs, takes off gown, hangs it on hook on cubicle wall, with the "contaminated" side out, scrubs hands and arms up to elbows, soaks in "clean" basin of disinfectant, dries on clean towel, and goes to next cubicle where each step of the procedure is repeated. After all infants have been fed, the bottles and nipples are scoured with hot suds, and rinsed, the inverted bottles in the rack are placed in the diet kitchen autoclave until they are sterilized the next morning.

Before the daily weighings the scales are wiped with a cloth wet with disinfectant solution. They are then balanced with a clean diaper. The student nurse puts on a cubicle gown, and places the stripped infant in the scoup. A square of clean paper is used to handle the weights, the weighed infant and diaper are placed in the crib, the infant is then bathed and dressed. After the washing of the hands (see feeding technique) the gown is placed on the cubicle hook, and the hands are again washed, a clean diaper is spread in the scoup. The student nurse then goes to the next cubicle and repeats each step of the procedure. Should the scales become contaminated, they are cleansed with disinfectant solution before they are used again.

The diet kitchen contains a gas-fired autoclave, gas range, kitchen sink with hot and cold water (foot-pedal faucets), kettles, deep sauce-

*Soiled diapers and linen soiled with feces are soaked in the pail of disinfectant in each room. Recently an aseptic diaper service delivers sterile diapers in tin containers each day and calls for all soiled diapers.

pans sieve funnels, and tagged wire bottle racks. A graduate nurse supervises the work of the student nurse who prepares the feedings. While the pyrex bottles rubber bottle caps nipples and utensils for measuring and mixing the food are autoclaved at 15 pounds for fifteen minutes the graduate nurse computes the amounts of the various ingredients required for the preparation of the twenty four hour supply of food for all infants. Most of the feedings are simple stock formulas, a card for each infant is in view on the wall. The student nurse measures weighs and mixes the ingredients and then puts on a long sleeved sterile gown mask cap and sterile rubber gloves. A sterile sheet is spread on the table, the hot bottles are removed from the autoclave lined up and covered with the sheet until they are filled. The strained food is boiled in deep saucepans for ten minutes measured into the sterile nursing bottles capped, and promptly refrigerated. The infant's name is written on each bottle with a blue glass pencil while bottles are warm. Or the bottles containing the measured feedings are covered with perforated rubber bottle caps autoclaved at 15 pounds for five minutes and then refrigerated.

The wet nurse station adjoining the diet kitchen is in charge of the diet kitchen nurse. An electric breast pump is used twice daily on lactating mothers of the vicinity who sell their milk. The strained pooled milk in sterile pyrex bottles is placed in a deep saucepan containing water up to the milk level after the water has boiled for twenty minutes the bottles are cooled and refrigerated.

DISCUSSION

Because two graduate and three student nurses for the twenty four hour care of twelve infants seemed excessive to several of the medical authorities acquainted with the Dick technic, the average cost per infant for the first and second six year periods has been computed. During the last six year period (with Dick technic) the cost per infant averaged 26 per cent less than it did with the standard technic. During the first six years the average number of occupied cribs was twenty eight during the last, it was twenty three. Because of the relative absence of illness most of the full term infants are now ready for adoption at the end of a month—the arbitrary minimum stay. Six hundred seventy eight more infants were cared for during the last six years than in the first six years. The admission of infants with enteritis from boarding homes and nurseries (where enteritis was present) without the occurrence of a secondary case at The Cradle in the last six years is proof that the Dick technic is flawless. To sterilize the food and not use an aseptic nursery technic is like an operating room in which only the instruments are sterilized.

SUMMARY

Vital statistics show that enteritis is still a prevalent cause of death in young infants. It spreads by way of contaminated food, nipples, and supplies. Anything intended for an institutional infant's nose or mouth should never be touched after it has been sterilized. The aseptic, individual nursery technic perfected by Dr. Gladys Dick in 1928 has made it possible to care for 1,620 homeless infants, without the occurrence of any cross-infection. It is sound economy because it reduces morbidity and prevents unnecessary deaths.

CONCLUSION

A six-year trial of the Dick diet kitchen and individual, aseptic nursery technic at The Cradle, without cross-infection enteritis, proves the technic flawless. The cost is not excessive. It is sound economy. The per capita cost per day is less than with the precautionary technic formerly used, without secondary cases of enteritis, the perennial morbidity is reduced, and there are no unnecessary deaths.

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MENINGOCOCCUS INFECTIONS

AN ANALYSIS OF 120 CASES IN CHILDREN

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THE purpose of this paper is to present in a statistical way the information obtained from a study of a series of 120 cases of meningococcus infections observed in the St. Louis Children's Hospital during the ten year period 1924 to 1934 in order that comparisons may be made with the observations in other localities.

Contact Infections—Although it is somewhat rare to observe more than a single case of meningococcus meningitis in a family five of our patients were definitely exposed to the disease by contact with another member of the family who had meningitis. In another case a brother had had meningitis eight months earlier.

Association With Other Disease—The possible relationship of the onset of meningococcus infection to upper respiratory disease is of some interest. Ten patients had had upper respiratory infection for at least one week before the onset of meningeal signs. Two patients had congenital heart disease, and two had rheumatic heart disease. One patient had had a skull fracture nine months before the attack of meningitis. The history of intracranial birth injury was obtained twice. The diagnosis of bronchopneumonia was made in three patients before they developed signs of meningococcus infection.

Duration of Disease—The average duration of illness before admission to the hospital was 5.4 days. However if the eleven cases which had become chronic are omitted the average duration would be only 3.5 days. The average stay in the hospital for the 120 patients was eighteen days. The average for the seventy-six patients who recovered was twenty-four days. It is of some interest to note that one patient remained in the hospital for six months because he was considered a carrier. He recovered from the attack of meningitis in about two weeks but meningococci were cultured repeatedly from the throat even after the tonsils and adenoids were removed. Finally the organisms were found to be nonvirulent and the patient was discharged. This was the only carrier diagnosed in our series. The average stay in the hospital for the forty-four patients who died was 7.3 days. If the three patients who had relapses are omitted the average would be five days. Patients in eighteen of the fatal cases died within twenty-four hours after admis-

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sion and obviously could have received very little treatment. Only thirteen patients of these forty-four fatal cases were in the hospital for more than two weeks.

Relative Frequency of Clinical Signs—The symptoms and signs observed with the percentage of frequency are given in Table I. In the last four the records were not complete.

TABLE I

SYMPTOM	PERCENTAGE PRESENT	CASES OBSERVED
Fever	99.2	120
Drowsiness	86.7	120
Neck rigidity	83.3	120
Vomiting	75.8	120
Headache (older children)	61.7	68
Unconsciousness	40.0	120
Convulsions	30.0	120
Chills	11.6	120
Strabismus	15.8	120
Abdominal pain	6.7	120
Positive Brudzinski reflex	68.4	79
Positive Kernig reflex	61.3	106
Absent abdominal reflexes	50.0	24
Deep reflexes		101
Normal	39.6	
Hyperactive	23.8	
Sluggish	20.8	
Absent	15.8	

The laboratory findings are given in the following tables.

TABLE II

SPINAL FLUID		WHITE BLOOD CELLS	
CELL COUNT	CASES	CELL COUNT	CASES
Under 1,000	20	Under 10,000	14
1 3,000	25	10 15,000	22
3 6,000	12	15 20,000	23
6 9,000	12	20 25,000	27
9 15,000	8	25 35,000	14
		Above 35,000	11

TABLE III

	AVERAGE	CASES OBSERVED
Polymorphonuclear cells in blood	76%	100
Polymorphonuclear cells in spinal fluid	88%	49

Urine

Albumin—(trace to ++, mostly trace) in 36 of the 93 cases (38.7%)

Sugar— in 2 of the 99 cases (2.2%)

Microscopic

White blood cells or casts— in 8 of the 91 cases (8.8%)

Meningococci found

Smear from spinal fluid 92 of 111 cases (82.9%)

Culture from spinal fluid 75 of 92 cases (81.5%)

Culture from blood 23 of 50 cases (46.0%)

Serum Treatment—Antimeningococcus serum was given routinely by the intraspinal route. In addition, many patients from the first received serum either intracisternally or intraventricularly, alternating with intraspinal therapy. If any difficulty was encountered particularly in cases of block, the serum was given repeatedly into the cistern or the lateral ventricles. Serum was given intravenously and intramuscularly in those cases in which it was thought septicemia was present because of skin petechiae or when the patient was seen soon after the onset of symptoms. It is a generally accepted fact that meningococcus meningitis is always preceded by a blood stream infection although this infection usually persists for only a short period of time. When serum was given intravenously, it was diluted with five to ten volumes of Ringer's solution and was given by gravity.

TABLE IV
ANTIMENINGOCOCCUS SERUM GIVEN

ROUTE	CASES	NUMBER OF INJECTIONS	AVERAGE AMOUNT	
			EACH INJECTION	EACH PATIENT
Intramuscular	12	24	14 c.c.	98 c.c.
Intravenous	2	8	21 c.c.	32 c.c.
Intrathecal	108	688	18 c.c.	114 c.c.

Serum sickness was observed in 64 of the 97 possible cases, an incidence of 64.9 per cent. The average time of appearance was the seventh day after the first injection of serum. When present it occurred between the fourth and twelfth days. The incidence of serum sickness in children under three years of age was about 12 per cent higher than in children over three years of age corrected for morbidity incidence. The usual manifestation was urticaria with an occasional slight elevation of temperature. Arthritis was noted in three patients.

Some immediate reaction followed the administration of serum to eleven patients. Five of these received serum intravenously and six intraspinally. Four types of reaction were observed after intravenous serum. Two patients became restless coughed, and collapsed but soon recovered. They had serum sickness on the sixth day. One patient had a chill and a rapid pulse. Accelerated serum sickness was observed once urticaria appearing in ten minutes after the serum and then again on the third day. One patient died a few minutes after serum was given into the longitudinal sinus. He had a convulsion and became cyanotic with shallow respirations. The cause of death could not be determined definitely as an autopsy was not permitted. Five patients reacted similarly after the injection of serum intraspinally. They collapsed and had irregular respirations and tachycardia but promptly improved. One of these patients had had no reaction after intravenous serum on the preceding day. One patient, who was moribund when admitted to

the hospital and had been ill for four days, died forty minutes after receiving serum intraspinally

Morbidity and Mortality—In this series of cases the morbidity incidence in females and males was identical. This observation leads to the conclusion that in children the disease is not more common in males than in females. In adults, the higher incidence in males probably may be explained on the basis of greater exposure and by the fact that many statistical reports deal with meningitis in army camps.

The incidence of the disease and the mortality, in relation to age are presented in Chart 1. The highest incidence was found during the first six months of life. In general this corresponds with the reports of other investigators. However, the diagnosis in infants is frequently more difficult to make than in older children, and for this reason many infants may have come to us without a diagnosis of meningitis, while some older

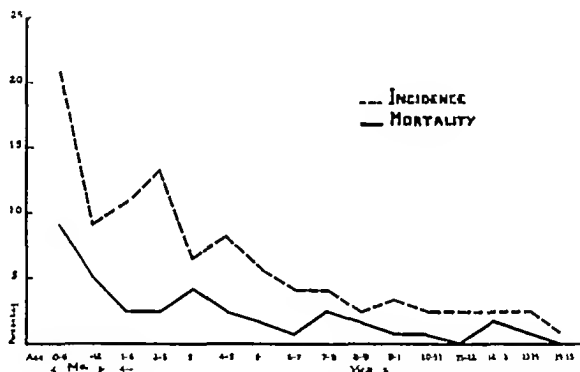


Chart 1—The relation of age to incidence and mortality in 120 cases of meningococcus meningitis.

children with a presumptive diagnosis were probably sent directly to the Isolation Hospital. Forty-four of the 120 cases terminated fatally, as a result of the infection, a mortality rate of 36.6 per cent. One patient was discharged unimproved in three weeks with a marked internal hydrocephalus, and one patient with obstructive hydrocephalus returned one month later and died. With these two cases included, the mortality rate would be 38.3 per cent. It is frequently stated that in children the highest mortality is during the first two years of life. The mortality rate in this series was 40.8 per cent for children under two years and 33.8 per cent for children over two years.

The number of cases reported in the city of St. Louis each year during the ten-year period is compared with the number of cases in the St. Louis Children's Hospital. The two curves correspond very closely and for each year are in a proportion of 8:1 (Chart 2). An epidemic occurred in 1929.

The incidence of the disease was most common during the winter and spring months, the highest incidence being in February and March (Chart 3)

The most important complications that developed were hydrocephalus, deafness, ocular disease, and otitis media. Bronchopneumonia was very infrequent even in the fatal cases in contrast to the usual reports. The diagnosis of hydrocephalus was made in nine cases, death resulting in

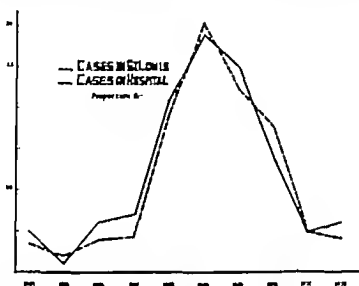


Chart 2.—Comparison of the number of cases of meningococcus meningitis in the city of St. Louis with the number of cases in the St. Louis Children's Hospital 1924 to 1934.

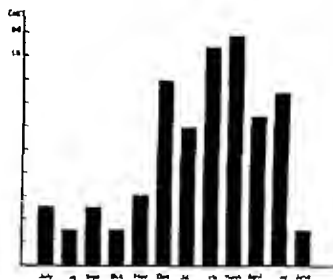


Chart 3.—Monthly incidence of 10 cases of meningococcus meningitis, 1924 to 1934

four. Definite obstruction was demonstrated in four patients and communication, in three. The type of hydrocephalus was not determined in the other two patients.

Eight cases of deafness were observed. Thus 10.5 per cent of the patients who recovered were deaf. This result is slightly high and no explanation can be given for it. The deafness was always permanent. The eye complications that were noted were iridocyclitis, iridochoroiditis, uveitis, iritis, and papilledema. The eyes were involved in twelve patients.

an incidence of 10 per cent Otitis media was present in 17.5 per cent of the patients

Three of the 120 patients had relapses and died, they were 5 months, 6 years, and 5 years of age The duration of the disease was nineteen, thirty-five, and seventy-four days, respectively Antimeningococcus serum was given on repeated occasions

Meningococcus septicemia without involvement of the meninges was observed in three patients Two of them recovered promptly after serum was given intravenously The third patient died sixteen hours after the onset of symptoms, 45 c.c. of serum were given intravenously, but this therapy was not beneficial The spinal fluid in four patients was found to be clear without an increase in the cell count, but meningococci were cultured from the spinal fluid and blood These cases were recorded as meningococcus septicemia with involvement of the meninges without cellular response They were treated, but all four died within twenty-four to forty-eight hours after onset of the illness

Petechiae were found in sixty-six patients, or 55 per cent, although in five of these records the nature of the skin lesions was questionable Petechiae were present in twenty-two of the twenty-three cases in which meningococci were cultured from the blood, or conversely only one positive blood culture was obtained where petechiae were not present Blood cultures taken from thirty-seven patients in whom petechiae were present were reported positive for meningococci in 59.4 per cent

Nine patients in this series were admitted to the hospital with a history suggestive of meningeal irritation for a period of three to four weeks The diagnosis of chronic meningitis will be used arbitrarily in the discussion of these cases They were not in any way comparable to the chronic basilar type of meningitis Most of these children presented a history of fever, vomiting, irritability, and rigidity of the back and neck, present for several weeks Seven of these patients responded very promptly to antimeningococcus serum therapy and apparently were well when discharged from the hospital Death occurred in two before more than three injections of serum could be given One patient returned one month after discharge and died Autopsy revealed a marked internal hydrocephalus but no evidence of meningitis All cultures were negative for meningococci at that time It is suggested from this study that a subacute or chronic infection of the meninges with the meningococcus is not uncommon and that the duration of the disease cannot be used as a clinical point in ruling out epidemic meningitis

Autopsies were performed in 47.7 per cent of the fatal cases

CONCLUSIONS

One hundred twenty cases of meningococcus infections occurring in the St. Louis Children's Hospital during the ten-year period, 1924 to 1934, are reviewed from a statistical standpoint with the following observations

- 1 The highest incidence was found during the first six months of life.
- 2 There was no difference in sex incidence
- 3 The disease was most common during the winter and spring months.
- 4 Meningococcus septicaemia without meningeal involvement was present in three patients two of whom recovered.
- 5 Chronic meningitis was present in nine patients.
- 6 Serum sickness occurred in 64.9 per cent of the patients
- 7 Relapses occurred in only three patients all of whom died
- 8 The mortality rate was 38.3 per cent

STREPTOCOCCUS MENINGITIS IN SCARLET FEVER

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THE diagnosis of suppurative meningitis in scarlet fever advanced from a status of opinion and sometimes conjecture to an approximation of fact when Hirsch¹ in 1900 first used lumbar puncture in differentiating the various cerebral manifestations that occur with this disease

Reported cases of scarlatinal meningitis undoubtedly fail to represent the actual frequency. With uncommon conditions of high fatality, the tendency is to report recovered cases and to neglect the others. Because streptococcus meningitis in scarlet fever is so uncommon, no ordinary group of patients with scarlet fever can give a satisfactory index of the actual frequency of the condition. The frequency and nature of streptococcus meningitis among 17,311 recent patients with scarlet fever is presented in this report, with the purpose of giving an approximate idea of present-day conditions. Collected reports of a number of observers, although having the value of significant numbers, do not have the reliability of a similar group from a single clinic.

All available records of scarlatinal meningitis were reviewed by Benard² in 1909. Fourteen cases were eliminated from his analysis because of incorrect diagnosis. Twenty-eight others were substantiated as meningitis. The clinical descriptions were adequate, and all had been confirmed by examination of the cerebrospinal fluid or by necropsy. This was considered the probable number of authentic reported instances of purulent meningitis in scarlet fever up to that time.

Nineteen additional cases have been reported since then, eleven³⁻⁵ without detailed description, eight by case reports.⁶⁻¹² Five of the nineteen patients recovered, those of Delger, Neal and Jones, Neal, Ohnacker, and one of Zischensky's. This is not representative of the usual fatality rate. Many fatal cases doubtless were not reported, perhaps several hundred in the course of the twenty-five years since Benard's review. His collected report of the observations of a number of investigators previous to 1909 showed the incidence of purulent streptococcus meningitis in scarlet fever to be nine cases among 13,550. Our series represents consecutive observations by the same persons from 1926 to 1933. The indicated frequency of the condition is somewhat greater, in that nineteen cases occurred among 17,311 patients with scarlet fever. Both

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series include only hospital patients. The frequency for scarlet fever in general would likely be less. Purulent leptomeningitis is certainly one of the rarer complications of scarlet fever, but it is important because of its high fatality.

ETIOLOGIC FACTORS

The age distribution of scarlet fever meningitis was not that of scarlet fever. Only two cases of meningitis occurred among 3566 patients less than five years of age. Patients aged five to nine years numbered 5539, 32 per cent of all patients with scarlet fever but this group included fifteen, or 79 per cent of those with meningitis. Since only one of the patients with meningitis was in the second decade and one in the age group twenty to twenty-nine years the frequency was less than would have been expected from the number of cases of scarlet fever in those age groups.

The distribution according to sex (eleven males and eight females) was in agreement with that for scarlet fever in which the number of males is slightly in excess of the number of females.

The seasonal distribution was like that of scarlet fever in this locality with the greatest number of cases in late winter and early spring and an annual peak of incidence in April and May. Sixteen of the meningitis cases were in the first six months of the year the time when scarlet fever is most common and complications referable to the nose and the ear most frequent.

Four patients presented initial symptoms of meningitis within ten days after the onset of scarlet fever and six between the eleventh and twentieth days. The interval for the other nine patients was more than twenty-one days. The longest interval was 117 days, the shortest, five days. The earliest reported onset of scarlatinal meningitis is on the fourth day¹³ of scarlet fever.

Eleven of the nineteen cases of purulent meningitis followed septic scarlet fever. Three were in the course of moderately severe infections and five in the course of moderate scarlatina. Only 31 per cent of all patients had septic scarlet fever but 58 per cent of those with meningitis were in this group. The frequency of meningitis among patients with mild scarlet fever was 0.05 per cent and among patients with septic infections 20 per cent. It is generally appreciated that all complications are more frequent with septic scarlet fever than with milder forms although of course, the severest complications can follow the mildest of original infections.

Meningitis was invariably secondary to a primary focus of infection usually adjacent to the meninges but sometimes remote. Thirteen cases occurred after suppurative otitis media and four through extension of infection from the paranasal sinuses. In two instances meningitis followed intermediate hematogenous distribution of the streptococcus from a local wound.

INVASION OF THE MENINGES

Infection of the meninges from the primary focus is either by way of the blood or lymph stream or by direct extension from adjacent structures. Meningitis of scarlet fever developing without a preceding suppurative complication has occasionally been reported. Forbes,⁷ commenting on a primary case without otitis media, admitted the possibility that postmortem examination would very likely have shown an intermediate focus of infection in the middle ear and felt that primary cases of scarlatinal meningitis would doubtless be reported less frequently if greater care were exercised in determining sources of infection at necropsy.

In a discussion of nasal paths of infection, Hajek¹⁴ considered that the usual process involved a spread of infection by tissue continuity through bone and dura and subsequent dissemination either by blood stream, by lymph stream, or by lymph channels along the olfactory nerves. Turner and Reynolds¹⁵ studied twenty cases of nonscarlatinal streptococcus meningitis originating from nasal infections. For eighteen the path of infection was traced through the osseous wall of chronically inflamed frontal (five) ethmoid (six), and sphenoid (seven) sinuses.

Invasion by way of the nasal accessory sinuses was responsible for four of the nineteen infections of the meninges in our group of patients with scarlet fever. Two also had an abscess of the frontal lobe of the brain without localizing signs. Headache and photophobia were outstanding symptoms. A typical example is presented.

CASE 1—Patient E. C., aged twenty years, became ill on Jan. 31, 1932, with complaints of severe frontal headache, tenderness referable to the eyes, moderate photophobia, and lacrimation. She developed sore throat, vomiting, fever, and headache on February 2. A typical scarlatiniform rash appeared on February 4. The usual evidences of moderately severe scarlet fever, together with bilateral conjunctivitis and slight edema of both eyelids, were present at the time of admission to the hospital, February 5. The areas over both maxillary sinuses were swollen. The maxillary swelling rapidly subsided, but infection of the ethmoid cells so progressed that the right eye was pushed forward and both eyelids became markedly edematous. The frontal headache, present since onset, increased progressively. The temperature on the first day in the hospital was 101° F., the pulse rate, 128, and respirations, 28 per minute. During the next three days the fever slowly but progressively increased to 102° F. A direct transfusion of 400 cc. of whole blood was given on the tenth day with no appreciable effect on the fever or improvement in the condition of the right eye. Examination disclosed a stiff neck and a positive Brudzinski sign. The headache increased in severity. There was a left lateral nystagmus. The swelling above the right eye increased and the area over the right frontal sinus was exquisitely tender. The deep tendon reflexes could not be obtained, tho Babinski and Kernig signs were positive. The cerebrospinal fluid was turbid and contained 8,000 cells per c.mm. of which 90 per cent were neutrophiles. The test for globulin was positive. Microscopic examination showed many gram positive cocci in chains. Hemolytic streptococci were identified in subsequent cultures. Death occurred on the thirteenth day of scarlet fever, fifteen days after the acute upper respiratory infection which immediately preceded the onset of scarlet

fever. The significant features at necropsy were abscess of the right frontal lobe, right purulent ethmoiditis and generalized purulent leptomeningitis (Chart 1).

In agreement with secondary meningitis generally, scarlet fever streptococcus meningitis was noted more frequently after otitic infection than after paranasal sinus disease. Thirteen instances of purulent meningitis occurred among 2,925 patients with scarlet fever and otitis media 380 of whom had surgical mastoiditis. Six cases developed relatively early in scarlet fever between the second and third weeks while seven were late in the disease from the fifth to the seventeenth week. In the following case otitis media appeared on the seventh day of scarlet fever, operation for mastoiditis on the fortieth day and meningitis on the sixty second day.

CASE 2.—Patient E. Z. a girl five years old, had a tonsillectomy on January 13. A generalized scarlatiniform rash appeared on January 10 and the family physician diagnosed the illness as scarlet fever. On admission to the hospital January 21

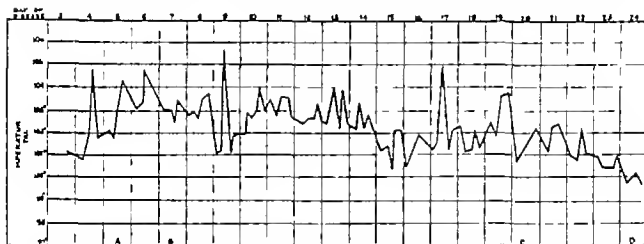


Chart 1—(Case 1) Paranasitis and meningitis in scarlet fever. A moderate scarlet rash, edema of eyelids, severe headache. B early paranasitis serosanguineous discharge from nose, persistent severe headache. C purulent meningitis. D death.

examination revealed a moderately ill child with a branny desquamation of the skin. The tongue had enlarged papillae and was completely peeled corresponding to scarlet fever of about a week's duration. The pharyngeal mucous membrane was reddened and the tonsillar fossae were covered with grayish white exudate. The surgical procedure nine days previously presumably accounted for this condition. The temperature was normal. A sharp rise in temperature to 102.4 F occurred the next day due to development of bilateral catarrhal otitis media and enlargement of a left cervical lymph node. The inflammation of the gland subsided within a few days, but the left ear began to discharge pus. The temperature did not return to normal until the twentieth day of illness. Subsequently the purulent discharge from the left ear diminished, and the clinical conditions became satisfactory. On the twenty sixth day there was fever of 101 F accompanied by an increased amount of purulent discharge from the left ear. This continued to be more or less profuse during the next two weeks, and there was always more or less fever. Complaint of pain related to the ear occurred several times when the discharge from the ear became scanty. On the thirty eighth day pain was first noted over the left mastoid process. This became increasingly more severe and left mastoidectomy was performed on the fortieth day. Postoperative convalescence was satisfactory in that the temperature receded to normal within four days and remained essentially so

for the succeeding ten days. On the fifty-fifth day the temperature rose abruptly, and the patient again complained of pain in the left ear. On the morning of the sixty-second day the patient was listless and drowsy and complained of a severe frontal headache. Vomiting was a distressing symptom. Neurologic examination was essentially negative except for sustained left ankle clonus. Lumbar puncture revealed a cloudy fluid under normal pressure. Cultures served to demonstrate hemolytic streptococci. Spinal drainage followed by intrathecal administration of polyvalent streptococcus antibacterial serum and streptococcus antitoxin was performed each day, but death occurred three days after the onset of meningitis. Necropsy disclosed a generalized purulent leptomeningitis (Chart 2).

Streptococcus meningitis of hematogenous origin from a remote focus is uncommonly rare. A case reported by Scholle¹⁸ followed a sup

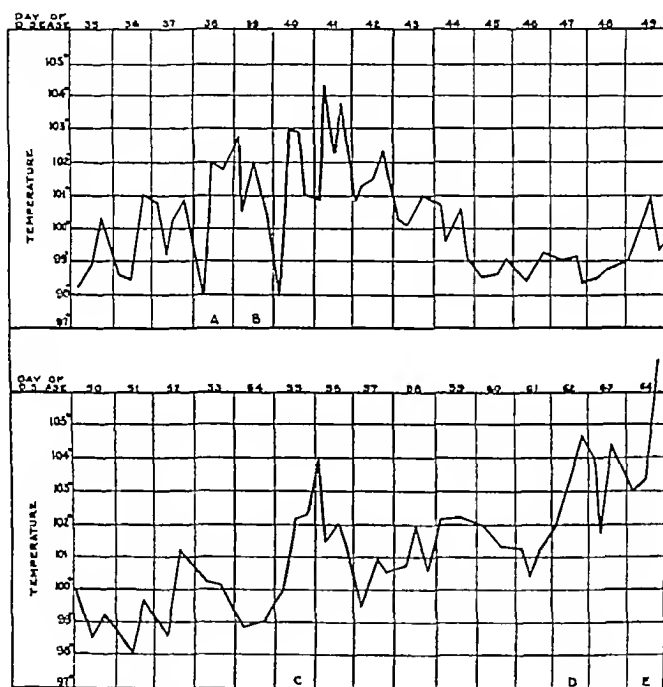


Chart 2—(Case 2) Otitic meningitis following moderate scarlet fever. A, left mastoiditis; B, mastoidectomy; C, pain in left ear and mastoid; D, purulent leptomeningitis; E, death.

purative knee joint. Another patient¹⁷ convalescent from scarlet fever sustained a head injury and developed clinical meningitis, confirmed by autopsy. Suppuration in a joint was the primary source of infection in two cases of this series. The first case was unusual in that traumatic injury of the knee preceded scarlet fever by ten days. There was localized infection in the joint, septicemia, and subsequent meningitis. The other patient had an infection of the joint on the fourth day of ordinary scarlet fever with generalized infection on the fifth day, of which meningitis was a part.

CASE 3—Patient R S., a boy seven years old, was admitted to the hospital March 21 four days after the onset of scarlet fever. The eruption of the skin was well pronounced and typical of scarlet fever. The temperature was 102.4 F the pulse rate 140 and the respirations, 32. About two weeks previously the patient had injured his left knee in a fall. One week later three days before the appearance of the rash of scarlet fever the knee and the entire leg became red and swollen. Shortly after admission to the hospital, curettement and free drainage for osteomyelitis showed much pus beneath the periosteum of the upper half of the tibia and necrosis throughout the length of the bone. The fourth day thereafter the patient was irritable, complained of headache and toward evening was delirious. The next day the fever was 104 F the patient was irrational and had stiffness of the neck. The cerebrospinal fluid contained 1080 cells per c mm. mostly neutrophiles, and numerous hemolytic streptococci. Repeated lumbar and cisternal punctures, with administration of scarlet fever streptococcus antitoxin were without benefit. Death occurred two days later ten days after the onset of scarlet fever. Toxins were prepared from strains of hemolytic streptococci isolated from the wound the throat and the cerebrospinal fluid. All were neutralized by scarlet fever streptococcus antitoxin, determined by skin test (Chart 3).

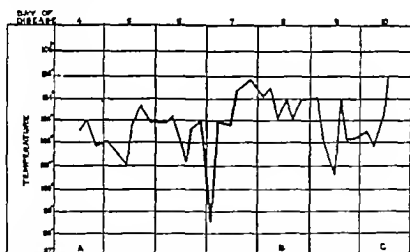


Chart 3—(Case 3) Acute osteomyelitis of upper end of left tibia and septic scarlet fever. A incision and drainage of left tibia. B purulent meningitis. C death.

Clinical Diagnosis—Few difficulties attend the clinical determination of frankly active meningitis. The rapidly developing illness the altered physical signs from meningeal irritation and the changes in the cerebrospinal fluid are prominent developments. The clinical patterns in the course of scarlet fever which suggest the possibility of impending meningitis are not as readily evident. Early surgical drainage of the primary focus of infection will be emphasized as the first requisite in the management of the actively developed condition. An appreciation of the kinds of infection and the successive train of clinical events which precede meningitis can indicate the need for operation under circumstances that might otherwise not be considered pertinent.

Secondary rhinitis and sinusitis are common late complications of scarlet fever but are singularly unattended by serious consequences. Scarletinal meningitis of nasal origin has been invariably related in this experience to profuse purulent or seropurulent nasal infections.

that develop coincidentally with the onset of the disease. The general illness corresponds to that form of scarlet fever described as septic Pansinusitis is almost always present. Acute suppurative ethmoiditis, with swelling of the eyelids and broadening of the root of the nose, is of serious moment and should suggest the danger of meningitis. If the swelling is localized at the inner canthus of the eye, the condition may appear more alarming, but the danger of meningitis is less since this indicates localization of the infection rather than extension. Lack of such localization, developing proptosis of the eye, increasing tenderness over the other sinuses, particularly the frontal, and complaint of extreme persistent headache with fever that lasts without remission for much more than five days are signs which indicate extension of the infection toward the meninges. In scarlet fever, meningitis after sinus infection is usually an early development, after otitis media, a late one. Progressive drowsiness with increased fever is a fairly certain indication of meningeal infection. Lack of response of the abdominal reflexes is one of the earliest physical signs, another is tenderness of the neck which often precedes actual rigidity.

The likelihood of meningitis in otitic conditions is more difficult to determine than with sinus infections. The condition can appear suddenly without warning. As a matter of cold experience, we have more than once entered a ward on a given morning to find a patient with definite meningitis, the suspicion of which had not even remotely been suggested the previous day.

A person who has once had otitis media and later contracts scarlet fever is not only more likely to have a second attack of middle ear disease but in our experience presents more than the usual probability of mastoiditis with intracranial complications. Mastoiditis after septic scarlet fever offers, in general, a greater possibility of secondary meningitis compared with the original infections of the mild toxic form.

An apparently benign otitis media with a normal temperature or low-grade fever, but with periodic rises accompanied by decreased purulent discharge, warrants serious attention. Tenderness over the mastoid process may be absent or indefinite. The mildness of the symptoms and the brief duration of the exacerbations suggest a conservative attitude toward mastoidectomy. Such conditions are potentially dangerous and operation should be performed with less than the usual indications.

Otitis media with progressively developing and definite infection of the mastoid cells presents far less danger in respect to intracranial complications. Mastoiditis with marked swelling over the mastoid process or anteriorly over the zygomatic cells, with edema of the superficial tissues, protrusion of the ear, much pain, much swelling and even subperiosteal abscess formation is likely to end well with adequate surgical management. There is evidenced a tendency toward localization, and the condition is comparable to the paranasal sinus infection which points

outward. A slowly developing but long-continued infection which tends to progress centrally without alarming fever, with little or no swelling or tenderness about the mastoid region and with indefinite constitutional reaction is cause for far more apprehension.

Meningitis in scarlet fever can occur as an aftermath of septicemia from a remote focus but commonly does not. Usual secondary localization in hemolytic streptococcus septicemia of scarlet fever is in the soft tissues of the body with formation of abscesses. Less commonly resolution occurs through localization in the joints in bone or in both hard and soft parts. Many instances of prolonged septicemia have been encountered in this series but only two terminated in meningitis. The interval between septicemia and meningitis was in both instances brief.

FATALITY OF SCARLATINAL MENINGITIS

A favorable outcome is infrequent with secondary meningitis of any sort. It is particularly uncommon with hemolytic streptococcus meningitis. In 1931 Rosenberg and Nottley¹⁹ collected records of forty one patients who had recovered from nonscarlatinal hemolytic streptococcus meningitis. Appelbaum¹⁰ in 1932 found two additional cases and added three of his own. These reviews did not include one recovery reported in 1927,⁶ three^{12, 20, 21} in 1930, and three^{22, 24} in 1931. The literature of 1932 contains seven,²⁵⁻³⁰ and three^{31, 33} appear in 1933 consequently in all there are now on record sixty three recoveries from streptococcus meningitis. The number of unreported recoveries can only be conjectured but probably is not great because recovery from this malady is uncommon enough to suggest reporting. Among the sixty three patients with streptococcus meningitis who recovered, six^{6, 10, 12, 24} had scarlet fever streptococcus meningitis. With one other case reported here the number of reported recoveries from scarlet fever meningitis is seven, and for all streptococcus meningitis sixty four.

CASE 4—Patient L. M., a boy aged five years, was admitted to the hospital Mar 18 1928 on the third day of scarlet fever the temperature being 101 F the pulse rate 100 and respirations 22. The next day the fever was 101 F and both tympanic membranes were injected the left bulging moderately. One therapeutic dose of scarlet fever streptococcus antitoxin was administered intramuscularly. Paracentesis of the left ear drum was performed March 20 with profuse discharge of pus. The temperature the next day was still about 104 F and toward evening the patient appeared listless. The neck was moderately stiff. On March 22 the general clinical condition was poor the patient was semicomatose and there was first noted redness and moderate swelling over the left mastoid. The Kernig Brudzinski Babinski, and Oppenheim signs were readily demonstrated. The deep tendon reflexes were absent bilateral ankle clonus was demonstrated. The cerebrospinal fluid was cloudy containing 18,000 cells per c. mm., with 80 per cent neutrophiles. Streptococci were obtained by bacteriologic examination of the fluid. The patient became rational after the lumbar puncture and seemed improved. Scarlet fever streptococcus antitoxin with polyvalent antibacterial streptococcus serum was given intravenously and subsequently repeated twice. Three

lumbar punctures during the next five days showed a decrease in the number of cells to 275, then 110, and lastly 20. Neutrophils predominated in the first two fluids, lymphocytes in the third. The opposite (right) ear meanwhile had started to drain spontaneously. The general clinical condition of the patient had been such that mastoidectomy was beyond consideration. On April 4 general improvement of the meningeal condition was such that bilateral mastoidectomy was chanced although the surgical risk was not good. The outer table of the bone was firm, but behind it free pus was found with extensive destruction of the inner plate. No sinus or dural exposure was necessary. The fever receded to normal April 9. Because of unsatisfactory progress, the mastoid wounds were reopened on April 23, a needle was inserted through the dura on the right side and much fluid under increased pressure was released. The brain substance in this area lacked normal consistency. Infected bone was removed from the left mastoid. Convalescence was subsequently uneventful. The patient was dismissed after seventy nine days in the hospital. Two years later he was still in good health (Chart 4).

Another patient with suspected but unproved secondary meningitis was also encountered in these observations. Recovery followed. The low

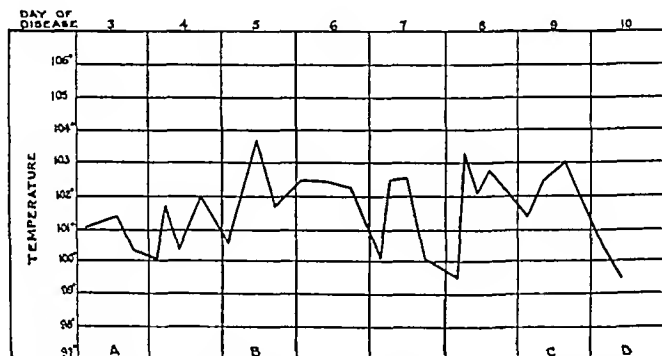


Chart 4—(Case 4) Septic scarlet fever. A suppurative otitis media. B left mastoiditis. C, bilateral mastoidectomy. D, convalescence ultimate recovery.

sugar content of the cerebrospinal fluid suggested an infectious origin, but this was not substantiated bacteriologically. The condition has been interpreted as serous meningitis, and the case is not included in this series. It is reported because of its singular interest.

CASE 5—A girl, six years old, was first seen on the fifth day of moderate scarlet fever. On the thirteenth day both middle ears discharged pus spontaneously, unattended by fever and without objective evidence of mastoid infection. In the fourth week the temperature increased, drainage from the infected ears was greater, but with no swelling or tenderness in the region of the mastoid process. On the thirty-sixth day of illness the patient was drowsy, irritable, with all of the classical signs of generalized meningeal infection. The cerebrospinal fluid was under pressure, and contained 1,080 cells, predominantly neutrophils. No infectious agent could be demonstrated microscopically or by culture. Shortly thereafter, 250 cc of whole blood was given by transfusion from a person recently recovered from scarlet fever, and 2 cc of streptococcus bacteriophage was injected intramuscularly, and 5 cc, intravenously. Three hours later bilateral mastoidectomy was performed, that evening lumbar puncture was repeated with injection of 5 cc.

of bacteriophage intrathecally. Intrathecal injections of bacteriophage were repeated twice on the second day and twice on the fourth day intravenous injections, in amounts of 10 c.c. on the second and fourth days. Thorough drainage of cerebrospinal fluid preceded each intrathecal injection. The number of cells did not exceed 1670 per c. mm. No infectious agent could be demonstrated although all fluids were examined. The sugar content of the cerebrospinal fluids was decreased

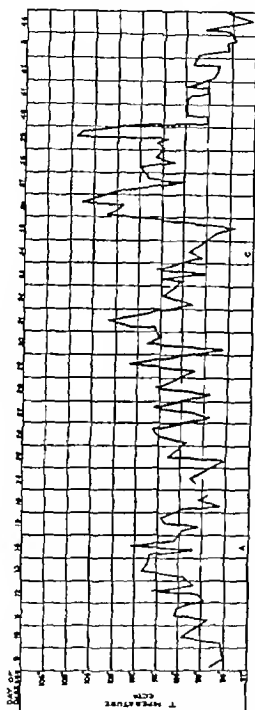


Chart 5—(Case 5) Moderate scarlet fever. A otitis media, B nine-day interval, normal temperature, free drainage from both ears. C moderate bilateral mastoid tenderness. D purulent meningitis. E convalescence, ultimate recovery.

to 30 mg per 100 ml. Immunotransfusion was repeated on the third day of meningitis. Ptosis of the left eyelid and strabismus were the only new clinical signs. There was progressive clinical improvement and the temperature declined. After the fifth day meningeal irritation was less marked and the temperature did not exceed 100 F. Convalescence continued uneventfully and the patient was released from the hospital on the eighty-fourth day of illness. Six weeks later there was no evidence of cranial nerve palsies and recovery was apparently complete. No clinical evidence is lacking that this was an instance of generalized meningitis after scarlet fever. Bacteriologic identification of an infectious agent was not ac

complished. Cultures of the aural discharge and from the mastoid wound contained hemolytic streptococci. It is interpreted as serous meningitis, although an infectious origin is possible (Chart 5).

The interval between the onset of meningitis and death is usually brief. Fourteen patients in our series expired within five days, and none survived more than nine days, other than the one who recovered. This short clinical course makes early institution of therapeutic measures essential if any benefit is to be expected. Kolmer has repeatedly emphasized the need for immediate early and adequate treatment, even drastic measures. An apparently unalarming clinical condition or a rational state at the onset of the condition does not permit delay because the course is invariably rapid.

TREATMENT

No specific therapeutic measure, nor even a satisfactory symptomatic method of management, has been developed for scarlet fever streptococcus meningitis. Antistreptococcus serums or chemotherapeutic agents do not compare in efficiency with the measures available for Type I pneumococcus meningitis, disappointing as they often are in that condition. Therapeutic suggestions are almost as numerous as the number of patients who have recovered. Many times a number of methods have been used in an individual case, thus making evaluation of any one impossible.

Accepted opinion is in agreement on the value of free drainage of the cerebrospinal fluid, though relieving symptoms due to pressure. Lumbar puncture is the commonest method, but of late cisternal puncture has often been practiced. The two may be alternated to advantage if the cerebrospinal fluid tends to become thick or organized through deposit of fibrin. Cisternal-spinal lavage with physiologic salt solution is of value under such circumstances. Various antibacterial streptococcus serums and scarlet fever streptococcus antitoxin have been administered intrathecally. Newer methods include the injection of Piegls' solution of iodine into the carotid arteries,^{26 35 37} usually combined with drainage of the cerebrospinal fluid by cisternal puncture, surgical drainage of the infected meninges by trephine or laminectomy,^{38 43} and various chemotherapeutic agents^{18 30 36 44} administered intrathecally with the purpose of sterilizing the cerebrospinal fluid.

The intrathecal administration of either antibacterial or antitoxic streptococcus serums has in our experience proved disappointing. Neal¹⁹ has seen two patients recover. The intracarotid injection of Piegls' solution of iodine or of serums, originally recommended by Kolmer,³⁰ has produced no demonstrable results. Nine patients with nonscarlatinal streptococcus meningitis and one with meningitis after scarlet fever were treated by this method. Eisner and Mendell²⁶ have recently reported two recoveries.

The methods of management used with this group of patients are presented in Table I. One patient recovered (Case 4). Polyvalent anti bacterial and antitoxic streptococcus serum was administered intravenously, combined with daily drainage of cerebrospinal fluid by lumbar puncture (Table I).

TABLE I
METHODS OF MANAGEMENT IN SCARLET FEVER STREPTOCOCCUS MENINGITIS

CEREBROSPINAL DRAINAGE	THERAPEUTIC AGENT	ROUTE	CASES	DEATHS	RECOVERIES
Lumbar puncture	None	-----	6	6	
Lumbar puncture	S. F. Strep. antitoxin and polyvalent antibacterial serum	Intravenous	1		1
Lumbar puncture	S. F. Strep. antitoxin	Intraspinal	2	2	
Lumbar puncture	Polyvalent strep antibacterial serum	Intraspinal	3	3	
Lumbar puncture	S. F. Strep. antitoxin	Intraspinal	1	1	
Lumbar puncture	S. F. Convalescent serum	Intramuscular			
Cisternal puncture	S. F. Strep. antitoxin	Intraspinal	1	1	
		Intracisternal			
		Intravenous			
Lumbar puncture	S. F. Strep. antitoxin	Intraspinal	2	2	
Cisternal puncture	Polyvalent strep anti bacterial serum	Intracisternal			
Lumbar puncture	Polyvalent strep antibacterial serum	Intraspinal	1	1	
Cisternal puncture	Immunotransfusion	Intracisternal			
		Intravenous			
Lumbar puncture	S. F. Strep. antitoxin	Intraspinal	1	1	
Cisternal puncture		Intracisternal			
		Intravenous			
	Polyvalent strep. antibacterial serum				
	Pregl's solution of iodine	Intracarotid			
Lumbar puncture	Antistreptococcic bacteriophage	Intraspinal	1	1	
Cisternal puncture	Immunotransfusion	Intracisternal			
		Intravenous			
Totals			10	18	1

The methods of management advocated by others and those which we have used permit but one conclusion namely that no single program of management exists which can regularly assure satisfactory results. None of the methods used has seemed to possess distinct advantages. Patients who recovered have been treated along widely dissimilar lines. From this experience with nineteen cases of scarlet fever meningitis and a larger group with nonscarlatinal streptococcus meningitis (sixty nine cases) certain general principles can be emphasized.

Perhaps the most important and certainly the first consideration is to determine the original focus of infection. This is sometimes difficult, and again is impossible, to attack surgically. However most infections of the leptomeninges in scarlet fever are secondary to middle ear disease in which operative measures may aid materially.

The second consideration involves attempted sterilization of the cir

culating blood. Meningitis may uncommonly be due to hematogenous infection. Much more frequently general sepsis is associated with meningitis, in which actual infection has been due to direct extension of infection from a local suppurative focus. The favorable results with immunotransfusion⁴⁵ in septicemic states of scarlet fever have influenced us to use that procedure when meningitis of scarlet fever is accompanied by streptococcus septicemia. That is not uncommon. Half of the patients had cultures of the blood containing hemolytic streptococci. Whole unaltered blood is given by transfusion from a patient recently recovered from scarlet fever.

Only after consideration of these two principles should attention be directed toward active treatment of the infected meninges. Repeated drainage of the spinal subarachnoid spaces is distinctly of value. This should be done daily, if necessary to relieve pressure, twice daily. The injection of antibacterial streptococcus serums and scarlet fever streptococcus antitoxin intrathecally has seemed to us to favor organization of exudate on the infected subarachnoid membranes to such an extent that actual blockage of circulation is not uncommon. Of late we have largely restricted measures to drainage combined with injection of air.

Streptococcus bacteriophage has been employed intrathecally in two cases, one, the unsubstantiated case (Case 5) with recovery, the other without demonstrable effect. We have been frankly skeptical of any value of these preparations in the treatment of infections. The clinical evidence is decidedly conflicting. Evans⁴⁶ contends that when bacteriophage comes in contact with body fluids, cells, or tissue debris, the lytic principle is inactivated. Kolmer and Rule⁴⁷ have recently treated experimental meningitis of rabbits by intracranial injection of anti-streptococcal bacteriophage. About one-third of the animals recovered.

SUMMARY

Purulent leptomeningitis is a very uncommon complication of scarlet fever. It is one of the commoner intracranial complications which are particularly rare in this disease. Of 17,311 consecutive hospital patients with scarlet fever, nineteen patients had generalized streptococcus meningitis.

Most instances of streptococcus meningitis originated from primary infection of the middle ear (thirteen), infected paranasal sinuses were a less common source (four), and two originated from localized suppurative infection of a joint, with subsequent hematogenous dissemination to the meninges.

The case fatality rate for scarlet fever meningitis is high. Only one of the nineteen patients in this series survived. Among the many patients reported by others in the course of years, only six are known to have recovered, seven in all.

No known therapeutic measure offers much promise. The prin-

ciples of management include removal of the original source of infection, attempted sterilization of the blood stream because general sepsis is often associated and finally attempted sterilization of the infected meninges.

Repeated drainage of the cerebrospinal fluid is a worthwhile procedure. Intrathecal administration of antistreptococcal serums and various chemotherapeutic agents has been disappointing.

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CONSTIPATION IN CHILDREN ITS EFFECTS UPON BODY MECHANISMS

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THE ills ascribed to an infrequent or inadequate emptying of the bowel have been many and varied. A casual survey of different textbooks on gastroenterology lists the following conditions which may at different times be more or less closely identified with constipation: vertigo, frontal headaches, neuritis, insomnia, bad dreams, inability to concentrate, hysteria, infantile convulsions, and other nervous phenomena. It is also stated that individuals suffering from chronic constipation not infrequently have a furred tongue, bad taste, foul breath, gaseous eructations, poor appetite, colicky pains, cold extremities, sallow complexion, skin affections, anemia, cardiac palpitation, and albuminuria. It still seems to be the opinion of some physicians and a majority of the lay public that an inadequate bowel evacuation can be the sole cause of fever and that an increased body temperature can be brought to normal by an enema or an active cathartic.

In our experience, limited entirely to infants and children, the causal relationship of such states as those described above to constipation has always seemed far-fetched, a careful study of the patient has usually revealed a more definite etiologic factor, and this statement is especially true of the relationship attributed to convulsions or fever and constipation.

The purpose of this paper is to record the observations in seventeen children in whom an evacuation of the bowel was either absent or inadequate during the course of a number of days. Twelve of these children were normal physically at the onset of the experiment, while the remaining five were suffering from some fever-producing disease at the onset and during the course of the experiment. Each child was first carefully observed during a control period of five days, a record being made of the temperature and pulse rate every two hours, the normal appetite, and mental state, laboratory studies during this period included a full blood count, sedimentation rate, blood chemistry and urine examination. When these data were obtained, constipation was brought about by the use of the deodorized tincture of opium, all other controllable factors in the child's diet and environment remaining unchanged. The observations reported above were then continued, the blood examinations being repeated every sixth day.

The ages of the children studied varied between four and twelve years the majority being in the older group. At the onset of the experiment, twelve of these children had apparently completely recovered from the infection which brought them to the hospital and had normal temperature for at least ten days or more. Nine of these children had originally been hospitalized for acute respiratory infections three had suffered from rheumatic fever and one, at the time of admission had infectious jaundice. All of the four children who still were acutely ill and febrile at the onset of the experiment were suffering from rheumatism and rheumatic carditis.

The number of days during which the effects of constipation were observed varied the shortest period of observation was sixteen days the longest sixty eight days the average period of observation for the sixteen cases was thirty six days. Complete obstipation was never obtained, every one of the subjects passed one or more small hard dry stools during the course of the experiment. On the average each child had one small bowel movement once in every eleven days however, two children went over twenty five days without any evacuation one being completely constipated for twenty nine days. It is interesting to note that to bring about these results large doses of a potent preparation of the deodorized tincture of opium were necessary constipation usually was not obtained until the child received 30 minims daily and at times as much as 75 minims daily were necessary. No untoward results were observed from the administration of what was formerly thought to be such a large dosage of an opiate for a child.

The children almost all appeared comfortable and happy during the course of the experiment. There was no complaint of headache lassitude bad taste gaseous eructations or other symptoms commonly associated with constipation. Their appetites may have been slightly decreased although this is a difficult factor to determine. However as a group they gained 18 pounds during the course of the experiment, or a little over 1 pound per child. (This weight was recorded at the completion of the experiment after the bowel had been thoroughly evacuated.) Many children did complain of some pains about the anus while passing a hard dry constipated stool and two of the older children had some lower abdominal discomfort toward the end of the experimental period both of these children were twelve year old girls, who had been made conscious that they were being artificially constipated this may have played a factor in their mental attitude and symptomatology.

An analysis of the objective findings of this group is as follows

Temperature—No effect whatsoever could be noted. In ten of the twelve children with normal temperatures at the onset of the experiment, the temperature continued unchanged throughout. In two children there was a rise in temperature caused by an intercurrent upper

respiratory infection, one of whom had fever ranging between 102° and 104° F for three days and the other, between 100° and 103° F for five days, in both of these children the period of constipation was continued during the course of their infection and for many days thereafter, and in both of these cases with the subsidence of the infection, the temperature dropped to normal and continued so thereafter

In the four children who were febrile at the onset of the experiment, no definite difference in the temperature curve could be noted while the experiment was in effect. When the period of constipation was stopped and an enema and cathartic administered, there was also no change from the regular fever curves previously noted.

The pulse rates were similarly unaffected.

Blood Count—Here also no definite changes were observed, the constipation apparently having no effect upon either the hemoglobin, the red cell count, the white cell count, or differential count. The average hemoglobin at the onset of the experiment was 82 per cent (Sahl) with 4,160,000 red blood cells. At the end of the period of constipation, the hemoglobin averaged 83 per cent and the red blood count 4,020,000.

Of the twelve afebrile cases, the average white blood count at the onset was 8,700 with 62 per cent polymorphonuclear cells, 33 per cent lymphocytes, and 5 per cent monocytes, included among the polymorphonuclear cells there were 2 per cent staff cells. At the end of the experiment the average white blood count was 8,400 with 60 per cent polymorphonuclear cells, 36 per cent lymphocytes, and 4 per cent monocytes, the number of staff cells remaining the same.

Sedimentation Rate—The blood sedimentation rate was similarly unaffected by constipation, no appreciable change being noted at any time in either the afebrile or febrile cases.

Blood Chemistry—Urea nitrogen, nonprotein nitrogen, and creatinine determinations were made in each case before, during, and at the end of the experiment. These figures remained normal and relatively unchanged throughout. In five cases the blood cholesterol was also determined, the average figures obtained at the onset of the experiment were 194 mg per 100 cc of blood, at the termination of the period of constipation this average had risen to 204 mg per 100 cc of blood, a slight change without any real significance.

Blood indican was determined in two cases, this also remained unchanged although the urinary indican increased considerably in the majority of cases. In one case at the onset of the experiment, the amount of indican recorded was 0.068 mg per 100 cc of blood, after forty-two days of constipation during which time the child had three small, hard, dry stools, the figure changed to 0.062 mg per 100 cc of

blood In the second case the blood indican at the onset of the experiment was recorded as 0.062 mg per 100 cc at the end of fifty days of constipation during which the child passed four small stools this figure had risen to 0.072 mg per 100 cc of blood

Urine—No appreciable change except the appearance of a more or less heavy trace of indican in the majority of cases was noted during these examinations One girl developed urinary frequency, probably due to the pressure of impacted feces in the rectum and lower bowel This was relieved after a thorough evacuation of the bowel No albuminuria was noted nor was there any evidence of an increase in the white blood cells.

Basal metabolism determinations were made in two cases at the onset of the experiment and during the latter period of constipation without any appreciable change

An x ray examination of the gastrointestinal tract in three cases revealed a similar picture in all of them normal gastric motility gaseous distention of the small intestine and a colon packed full of feces

SUMMARY AND CONCLUSIONS

A study of sixteen cases of artificially produced constipation in twelve children who were well and in four who were subacutely or chronically ill revealed no definite changes, either from the subjective or the objective standpoint.

As far as could be determined from physical examination, temperature charts complete blood analyses, and urinary examinations no demonstrable changes occur in rather severe chronic constipation in children

The temperature charts were especially striking At no time could any rise in temperature be associated with constipation, in two children who developed definite acute respiratory infections and fever during the course of the experiment the temperature subsided and then continued normal even though no bowel movement occurred during the illness and for many days thereafter Furthermore a thorough bowel evacuation at the end of the period of constipation produced no changes upon the average temperature curves in those children who were ill and febrile throughout the experiment

Thus it can be said with a fair degree of certainty that an infrequent or inadequate bowel evacuation cannot experimentally be demonstrated as producing harmful effects in children

MASKED HYPOTHYROIDISM IN CHILDREN

OSSEOUS DEVELOPMENT AS AN AID IN DIAGNOSIS

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A STATISTICAL analysis of a group of 500 children sent to the clinic for endocrine study revealed 15 per cent to be hypothyroid in a masked state. The presence of this condition in such a comparatively large number of children prompts the presentation of this protocol. It is hoped that the few cases to be presented here will add to the already mounting literature on the subject, especially to the arguments of Shelton^{1, 2} and Cattell.³

The term "masked" is used to indicate a condition which offhand does not point to hypothyroidism and which therefore may go unrecognized unless carefully studied and interpreted. While the signs and symptoms of classic cretinism and marked hypothyroidism present an easily recognizable type, the picture of mild hypothyroidism often goes unrecognized because the complaints of the patient are misleading and often are misinterpreted.

In the cases to be cited, ordinary therapy administered for the complaints of the patient and not for the real cause, such as laxatives for constipation or ointments for eczema, brought little benefit. A thorough study of the past and present history was therefore made with the view of bringing to light other or more hidden symptoms, such as tardiness in walking, talking or teething, stunted body growth, genital hypoplasia or poor mental response. These symptoms, in addition to the complaints enumerated by the patient, were the means of detecting the hypothyroidism. As will be seen in the cases to be cited later, not all of the symptoms listed above appeared in every case—often only one or two of these existed—but even only one or two of these were considered sufficient clues for further study. As early as 1913, Leopold-Levi and Rotschild,⁴ Leopold-Levi,⁵ and Heitoghe⁶ associated several of the above clinical symptoms with a subthyroid state.

A final diagnosis of mild or masked hypothyroidism was based primarily on

1. A history of either physical retardation or of mental retardation, or a combination of both

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2 The existence of signs and symptoms akin to the symptoms of the classic cretin or marked hypothyroid however these symptoms were apparent in a much milder degree

3 The presence in a varying degree of delay in the unfolding of the osseous framework as revealed by roentgenograms

This latter condition delay in the unfolding of the osseous framework, was carefully studied and was considered to be of definite diagnostic importance. Although the osseous development of the cretin as revealed by the roentgenogram has been studied for some time the same study of the osseous unfolding has not been sufficiently considered for the recognition of the mild or borderline case. All children who presented any suspicion of hypothyroidism were subjected to a thorough roentgen ray study of the bony framework. The presence of any bony retardation as revealed by this study was accepted as confirmatory evidence of hypothyroidism providing that rickets, mongolism, celiac disease, juvenile congenital syphilis and Cooley's erythroblastic anemia were eliminated.

In those cases in which the hypothyroidism was of too recent onset to make osseous retardation roentgenographically apparent, a basal metabolic test was made whenever the child was old enough to cooperate. With children who were too young for a metabolic test and yet showed clinical evidence of a recent onset of thyroid insufficiency thyroid medication was administered and was found to be efficacious. The recent observations of Topper⁷ are of interest in this connection. She reported the effect of thyroid therapy on children selected because of retardation in mental or physical development without an obvious defect in the function of their thyroid gland. The findings show that thyroid administration markedly stimulated the growth and development of these children even though in some cases the basal metabolic rate was normal. Dentition, mentality, growth in height and osseous development were improved by thyroid therapy in those who showed evidence of retarded development. It is my belief that Topper's cases may have fallen under the classification of masked hypothyroidism for in addition to the findings of mental or physical retardation these children suffered from osseous retardation which responded to thyroid therapy.

It must be pointed out that while all of the cases in this series have been diagnosed as 'masked' or mild hypothyroidism other factors (at present not definite) may be responsible for the osseous retardation. Some of these conditions have been mentioned above.

RÉSUMÉ MASKED HYPOTHYROIDISM WITH RETARDED OSSEOUS DEVELOPMENT

1. Incidence in a series of 500 cases referred for an endocrine study 15%
2. Number of cases in this series—40

Males	60%
Females	40%

3	Familial	35%
4	Height	
	Repressed height	60%
	Normal range	25%
	Accelerated height	15%
5	Weight	
	Underweight	34%
	Normal range	38%
	Overweight	28%
6	Genital development (males)	
	Normal testes	15%
	Hypoplastic testes 45%	} 85%
	Undescended testes 40% (unilateral or bilateral)	
7	Bowels	
	Normal	44%
	Constipated	34%
	Sluggish	22%
8	Mentality	
	Retarded	32.5%
	Fair	27.5%
	Good or bright	32.5%
	Excellent	7.5%
9	Nervous and emotional tendencies	
	Apathetic	25%
	Unstable { irritable, bad stubborn, spiteful }	28%
	Restless and poor sleepers	9%
	Active and alert	38%
10	Skin	
	Dry	50%
	Normal	50%
11	Hair	
	Dry or poor luster	65%
	Normal	35%
12	Laboratory Findings	
	(calcium (9 cases)—range 9.1 to 13.6 mg	
	Phosphates (5 cases)—range 4 to 6.5 mg	
	(cholesterol (6 cases)—range 100 to 210 mg	
	Basal metabolic rates (9 cases)	-23% to -4%

CASE 1—A M., a girl, aged six years eight months, was referred Apr 12, 1932, with a history of dryness, itching, and hardening of the skin. This condition had persisted since she was six months old. Another child in the family also has a tendency toward this type of skin condition.

On examination it was found that the patient weighed 41 pounds (average normal, 40.7 to 50.8) and was 45 inches tall (average normal, 44.7 to 47.8).⁸ There was marked dryness, toughness, and scaling of the skin with scratch marks and excoriations. The skin was wrinkled, leathery, and thick over most of the body. The hair was dry, sparse, and lusterless. The facies, presenting a prominent forehead and somewhat widely spaced eyes, was slightly suggestive of the cretinoid type. The patient, apparently, was not dull but not very cooperative. The basal metabolic rate was minus 14 percent (test fairly satisfactory). Roentgenograms of the wrist and hands showed the presence of seven small carpals.⁹ The distal epiphysis

of the ulna was present but small. Since the patient was a female and showed poor maturing, it was felt that she was from eight to twelve months retarded in bone development. In view of the above findings, a diagnosis of mild hypothyroidism together with a moderate degree of ichthyosis was made.

The patient was put on a standard brand of thyroid substance varying from 1 to 5 grains daily. She did not begin to show a response to treatment until after the larger doses were administered. On June 29, 1932 two and one-half months after the institution of this treatment, the following note was recorded: 'Skin much improved and apparently taking on a moist feel, the hair has a better luster but is still dry the skin is not wrinkled as previously and is clearer.' Prior to this time, according to the patient's mother the skin had always been the same there were no marked remissions, in spite of different ointments administered from time to time. On Feb. 28, 1933, the patient was examined again. At this time her condition was noted as satisfactory although the skin of the hands was still dry. A basal metabolic rate showed a plus 20 per cent. In April, 1933 one year after treatment was instituted, the height was 49 inches and the weight 48 pounds (an increase of 3 inches, and 7 pounds). The patient discontinued visiting the clinic.

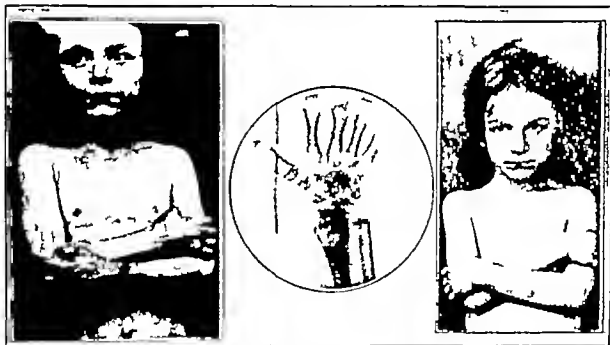


FIG. 1.—Case 1. A. Patient at the age of six years and nine months, Apr. 9 1932. B. Roentgenogram of bones of hand at same age, Apr. 13 1932. C. Patient at age of seven years and three months Nov. 1932.

About one year later Jan. 23 1934 a visit was made to the patient's home. She was found to be generally well. There had been a gain in height and weight in spite of the fact that thyroid substitution had been neglected in the interim. The child had not had an acute exacerbation of her skin condition. However casual examination showed a return of some of the dryness and leatherlike skin about the legs and knees, hands and forearms. The itching and excoriations had not recurred. Altogether her condition was much better than at the first examination.

Fox¹⁰ believes ichthyosis to be a congenital malformation of the skin of unknown cause although certain facts point to an endocrine etiology. Porter¹¹ however associates ichthyosis with hypothyroidism. In his series of ten cases in children ranging from eight to twelve years of age, he found 70 per cent with a basal metabolic rate below normal,

10 per cent above normal, and 20 per cent normal. In his treatment of these cases he noted that those who derived the greatest benefit from thyroid administration were those with the lower basal metabolic rates, while those with the normal or above normal rates derived little benefit. Although Porter's suggestion of treating cases of ichthyosis accompanied by low basal metabolic rates with thyroid therapy is important, it is not always possible, as has already been pointed out, to obtain basal metabolic rates in younger children. In such cases it has been suggested that a study of the osseous development be made, and, if the bone study reveals osseous retardation, thyroid substance in large doses should be instituted. I have recently encountered a number of children presenting osseous retardation who are suffering from

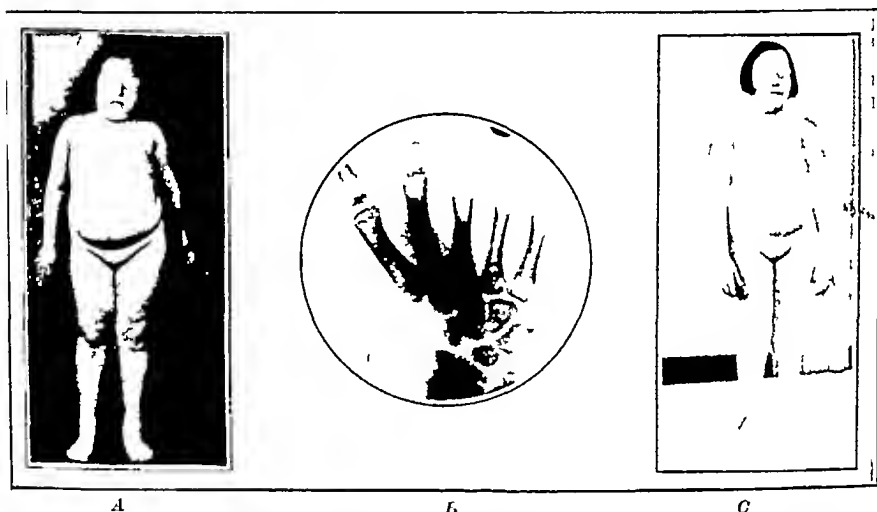


Fig. 2—Case 2. A, Patient at the age of eight years, Nov. 22, 1932. B, Roentgenogram taken Nov. 25, 1933, patient aged nine years. C, Patient at the age of nine years and four months, March, 1934.

marked chronic eczema since early infancy. Thyroid substitution seems promising in a number of these.

CASE 2—Mu S., a girl, eight years four months of age, was referred for obesity. The infantile history was not significant except that she started walking at fifteen months and then developed pertussis and stopped walking until the age of twenty-two months. She was said to have had a mild case of rickets. At the time of examination she presented a marked giraffe obesity, a short neck and increased supraclavicular and nuchal fat paddings. The posture was poor, there was a lordosis, bilateral pes planus, and a markedly relaxed and protuberant abdomen. The skin of her face was puffy and somewhat thickened. Her hair and skin were not dry. The weight was 87 pounds (average normal, 47.6 to 59.2), the height was 48 inches (average normal, 47.5 to 50.9). The patient was an average student at school although she was said to be sluggish at home. She was severely constipated.

The basal metabolic rate was minus 14 per cent. Roentgenograms of her wrists and hands showed the presence of seven poorly massed carpal bones. The distal

ular epiphysis was present. There was a bone retardation of one year. A diagnosis of mild hypothyroidism was made.

Thyroid substance ranging up to $2\frac{1}{2}$ grains per day was prescribed. Marked general improvement was noted. The facial expression became brighter, the patient became more alert, there was marked thinning out of the fat with a marked loss of fat in the nuchal and supraclavicular regions, the abdomen became less prominent.

At the end of ten months of treatment (at the age of nine years two months) the patient had gained $2\frac{1}{2}$ inches in height and had lost 3 pounds in weight. Roentgenograms of the wrists and hands showed a better massing of the previously existing carpsals, although these were still smaller than the average normal. The elbow showed an absence of the trochlea, the presence of which is normal at nine years. In all, she still showed a bone retardation of about six months.

CASE 3—J. S., a white male child seven years nine months old, had been treated in the general clinic since birth and was referred to the endocrine clinic for genital underdevelopment.

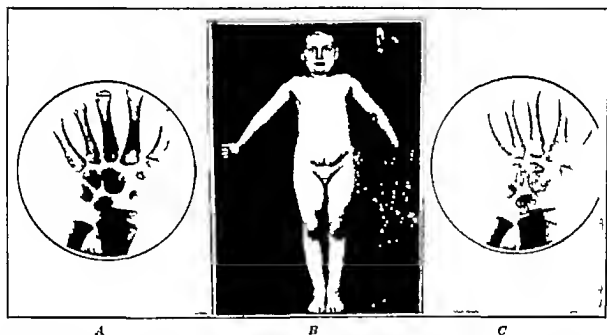


Fig. 3.—Case 3. A, Roentgenogram of bones of hand, patient seven years nine months old. B, Patient aged seven years six months, July 3, 1932. C, Roentgenogram of hand, Nov. 10, 1932 (patient aged eight years and nine months).

The patient's birth weight was $8\frac{1}{2}$ pounds. He cut his first tooth at ten months and started talking at an early age. He had received cod liver oil for a number of years, and his diet had been prescribed in the children's clinic. The patient had had no illnesses except mild upper respiratory infections and bronchitis. He was also said to have had bowing of the legs in early infancy. There was a slight eczematous condition of the face during his infancy.

Physical examination at the age of seven years nine months showed the weight to be 83.5 pounds (average normal 46.1 to 51), the height 46 inches (average normal, 47 to 50.3). The patient was obese. His hair was dry, lusterless, wiry and stumpy. The left testis could not be felt and the right testis was very small and retracted in the canal (these findings had been noted on the patient's record since the child was one year of age). At the age of four years the patient was examined by a surgeon who was able to pull down both testes but who said they were very small. Later, however, several careful examinations failed to reveal the presence of the left testis.

The basal metabolic rate was minus 14 per cent. The blood chemistry was as follows: cholesterol, 165 mg, calcium, 13.2. The Wassermann reaction was negative. Roentgenograms of the wrist showed the presence of seven carpals, four of fair size and three very small. The distal epiphysis of the ulna was absent (present normally at six years). He was therefore retarded in osseous development from eighteen to twenty-four months. In view of the bone retardation, the lowered metabolic rate, the hypoplastic genitals, the obesity, the dry, stumpy, and lusterless hair, and the presence of a somewhat dulled mentality, a diagnosis of mild hypothyroidism was made.

Thyroid substance ranging from $1\frac{1}{2}$ to 3 grains daily was administered for a period of one year. After this time there was marked improvement in his bone development, there being seven well formed carpals in each wrist and a small distal ulnar epiphysis. The bone development, however, was still somewhat retarded. In addition to these findings his hair became fine, silky, and took on a good luster. Both testes, though small, had descended lower down the canal. The patient

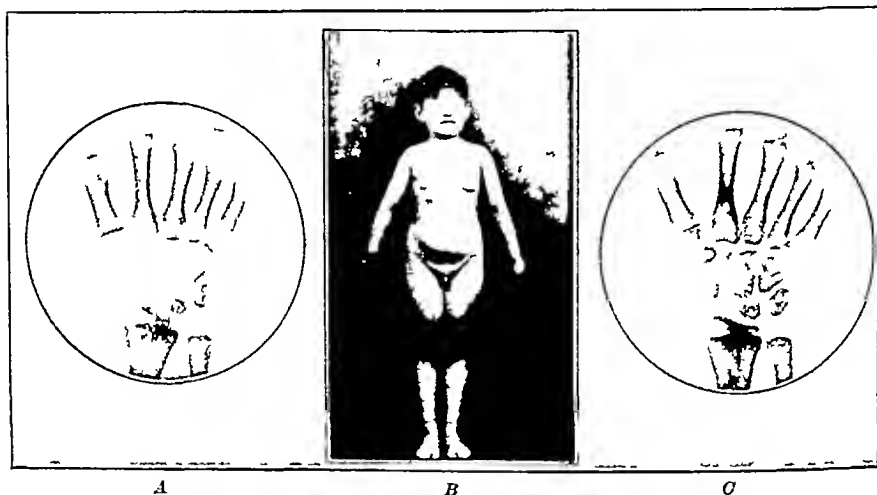


Fig 4—Case 4. A, Roentgenogram of bones of hand, patient aged seven years, Apr. 20, 1932. B, Patient at the age of seven years, May 2, 1932. C, Roentgenogram of bones of hand, Oct. 7, 1933, patient aged eight years and four months.

was brighter and more active and was less forgetful than previously. He had gained $3\frac{1}{2}$ inches in height during the year of treatment.

CASE 4—My S, a white male child, seven years old, was referred because of undescended testes.

The patient's infantile history was normal as regards development. His birth weight was 8 pounds 11 ounces after a full term normal delivery. He had had scarlet fever, measles, pertussis, and occasional colds. He had had and still was troubled by an eczematous rash behind the ears. It was felt by the mother that this came "after eating eggs." His diet was good and varied. The patient's parents were both very intelligent, and the boy's mentality was excellent, as evidenced by a good school record and extracurricular activities.

On examination (Apr. 19, 1932) the patient was found to be 49.5 inches in height (average normal, 45.6 to 48.8) and weighed 64 pounds (average normal, 43 to 53.2). There was slight girdle obesity. The teeth were normal, the hair and skin were not dry. The patient was troubled with chronic constipation. The testes were not felt except for a suggestion of a slight mushy mass in the left inguinal canal. The penis

was small. Blood analysis showed cholesterol, 165 mg calcium 10.4 phosphorus, 5.2 fasting sugar, 95, creatinine, 1.2 urea nitrogen, 12. The urine showed a faint trace of albumin. The basal metabolic rate was minus 18 per cent. The bone development at seven years of age showed the presence of five small carpal centers in one wrist and six in the other. The distal epiphysis of the ulna was absent. Osseous development was retarded about twenty four months. The sella turcica was normal.

The outstanding findings were moderate girdle obesity cryptorchidism, high periodic eczema, low basal metabolic rate and retarded osseous development all of which enabled a diagnosis to be made of mild thyroid insufficiency.

Thyroid substance ranging from 0.5 to 1 grain daily was administered. In addition to the thyroid therapy, the patient was placed for a short time on antuitrin and then on anterior pituitary like hormone 1 c.c. two to three times weekly hypodermically.¹² At the end of sixteen months of treatment he showed a filling out of the scrotum and the presence of two small pea sized testes high up in the canal. A basal metabolic rate taken at this time was plus 1 per cent. The patient had also gained 3 1/4 inches in height during this period. Roentgenograms of his bones showed the presence of seven well formed carpal centers instead of the five small ones formerly observed, however the distal ulnar epiphyses were still absent. Osseous development was still retarded about ten to twelve months.

Stockard¹³ emphasized that there is a great deal of evidence to show that the amount or quality of thyroid secretion present in the developing individual is an important factor in determining the rate of growth. The thyroid hormone affects the growth rate, primarily by determining or affecting the rate of metabolism.

While it can be said that the majority of these patients are short in stature, it is apparent, as seen in the case reported above, that some of them fall within the average normal standards of height for their age in spite of an apparent thyroid insufficiency. It has been shown that there can be increased growth in thyroidectomized tadpoles even though differentiation as evidenced by metamorphosis is absent.¹⁴

The opinion is held that some cases of genital underdevelopment presenting undescended or hypoplastic testes may be attributed to thyroid deficiency. Dorff¹⁵ has reported a number of such cases showing retarded osseous development in addition to their underdeveloped genitals and is of the opinion that this genital hypoplasia in such children is secondary to a thyroid insufficiency. Thyroid substitution is of apparent benefit in this type of child. However I believe that the anterior pituitary like hormone supplementing the thyroid substitution enhanced the result in Case 4. It should be mentioned that thyroid substitution alone will stimulate definitely the hypoplastic genitals present in this type of patient although not nearly as rapidly nor as spectacularly as with the anterior pituitary like hormone.¹⁵

CASE 5—G. T., a white female child, seven and one-half years of age, was examined in the general pediatric clinic on Apr. 1, 1932, because of small stature, dull mentality, dry hair, dental caries, and enlarged tonsils. She weighed 39 pounds (average normal, 44.1 to 54.9) and her height was 42.5 inches (average normal 46.3 to 49.5). The diagnosis was infantilism, for which the patient was referred to

the endocrine clinic. It was reported that the patient was of a full term normal delivery, the birth weight being 9 pounds. The first tooth appeared at eight months of age. She walked at one year and talked at the normal time. The patient was breast fed for eleven months and had not received cod liver oil until the age of three years. She had had measles and pertussis, she had suffered from occasional enuresis and constipation.

Blood analysis showed calcium, 13.6 mg, fasting sugar, 125 mg, nonprotein nitrogen, 36. The Wassermann reaction was negative. The urine showed a trace of albumin. The basal metabolic test was unsatisfactory. The intelligence quotient (Stanford Binet) was 99, the examiner noted, "Child's manner leads me to believe she would do better on the performance type test." X-ray examination at seven and one-half years of age showed the presence of six carpal centers in one hand and seven in the other, of which only two were of fair size. The distal epiphysis of the ulna and the epiphysis for the head of the radius were absent (normally present at age of five years). There was bone retardation of twenty-four to thirty months. The sella turcica was normal.

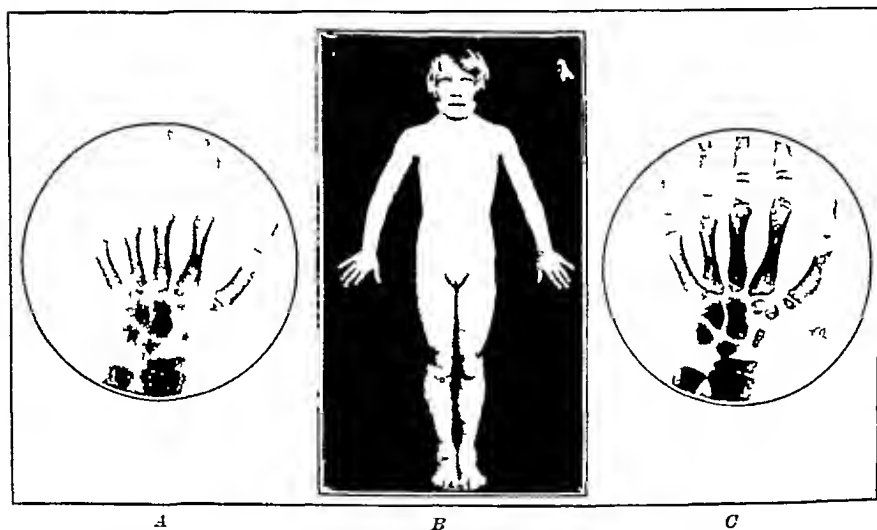


Fig 5—Case 5. A, Roentgenogram of bones of hand patient aged seven years and six months Apr 9 1932. B, Patient at the age of nine years and four months Jun 20 1934. C, Roentgenogram of bones of hand patient aged nine years and four months Jan. 20 1934.

A diagnosis of mild hypothyroidism was made, and 0.5 grain of thyroid substance daily was started. This medication was regularly taken for about six weeks and then discontinued by the patient. It was not until almost two years later, Jan 18, 1934 that the patient was again presented. On this examination, after a two year period without treatment, the objective symptoms were more pronounced. There were prominent thickened cretinoid features, with puffiness under the eyes, the skin and hair were dry and lusterless. There was a tendency to keep the mouth open and to protrude the tongue. The mother said the patient's responses were poor, that she forgot easily and that she was slow in school. This latter fact was also mentioned at the first examination, although the patient was otherwise active. The mother thought that when the child took the thyroid substance she was much brighter. The patient's weight at this time was 44.75 pounds (average normal, 53 to 66), height 45.5 inches (average normal, 49.9 to 53.2). She had gained 3 inches in height and 5.75 pounds in weight in two years. Roentgen ray examination of the bones

(at age of nine years four months) showed some improvement over the original condition there were seven carpals of fair size though these were definitely smaller and more poorly massed than in the average normal. The distal epiphysis of the ulna, the size of a pinpoint, was present. There was also retardation of the epiphysis at the head of the radius which was just appearing. Osseous development at this time was more retarded than at the first examination. The retardation was equivalent to about thirty six to forty two months. The sella turcica was normal.

This case illustrates several important points. A diagnosis of mild hypothyroidism was made two years previous to the administration of intensive thyroid treatment. The patient presented evidence of retarded ossification and other characteristics pointing to the diagnosis. At the end of two years the symptoms became much more pronounced tending toward the cretinoid type and although her bone age advanced somewhat it still lagged far behind the increment in her chronologic age. It was apparent that there was no spontaneous correction of the osseous retardation in this case.

Shelton's report^{1, 2} of three siblings all presenting retarded ossification revealed that two of these siblings showed rapid carpal development and general somatic growth under thyroid therapy within a short period while the third child who received no treatment advanced only slightly in bone age. In addition the control patient also lagged far behind in the optimal increment in height and weight. It appears obvious then that such cases incompletely treated fall short of fulfilling their normal destiny.

SUMMARY

1 A series of forty cases from a group of 500 children submitted for endocrine study formed the basis of this report.

2 The mental or physical retardation or both in these children appeared akin to the same but more severe findings of sporadic cretinism and marked hypothyroidism.

3 This condition I would term masked hypothyroidism since the symptoms are misleading and often go unrecognized unless properly studied and interpreted. Careful questioning frequently discloses a chain of symptoms other than those of which the patient complains. When considered with poor somatic development and retarded osseous unfolding the findings are significant.

4 Retarded osseous development may be evidenced by the late appearance or poor massing of ossification centers and epiphyseal nuclei. Such retardation was a most important factor in our diagnosis of hypothyroidism—mild as well as marked states.

5 In cases in which the hypothyroidism was of too recent occurrence to be demonstrated roentgenographically other diagnostic measures were employed in children over eight years of age, who were cooperative a basal metabolic test was performed. If it was low, it

was considered as confirmatory evidence of hypothyroidism. In children under eight years of age, a basal metabolic rate was usually not informative.

6 Thyroid therapy was efficacious in cases in which, in addition to evidence of physical or mental retardation, there was (1) osseous delay, (2) a low basal metabolic rate, and (3) no response to other forms of treatment for the alleviation of the complaint or combination of complaints.

Acknowledgment is made to Dr Mendel Jacoby, director of the pathology department of the Beth El Hospital, for suggestions in compiling this report.

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1176 EASTERN PARKWAY

THE ANTIRACHITIC VALUE OF IRRADIATED EVAPORATED MILK IN INFANTS

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THIS investigation was made to determine the antirachitic value for infants of directly irradiated evaporated milk. The studies of Hess and Lewis¹ and Mitchell, Eiman, Whipple and Stokes² indicated clearly that the vitamin D content of fortified milks determined by rat assay gave no clear indication of their clinical potency; thus Hess and Lewis found that directly irradiated milk milk from cows fed irradiated yeast (so-called "yeast milk") and viosterol all containing the same number of rat units of vitamin D differed widely in their antirachitic value for infants. Hess and Lewis stated that the ratios of human antirachitic potency of these substances in the order named was 15:8:1; in other words, 15 rat units of viosterol have the same antirachitic action in the infant as 8 rat units of yeast milk or 1 rat unit of directly irradiated milk. In a recent critical review of the literature on vitamin D milk, additional evidence has been collected concerning this variability in human antirachitic activity of fortified milks containing the same number of rat units of vitamin D.³ Obviously, in the present state of our knowledge the only true evaluation of antirachitic potency for infants of a new vitamin D fortified milk must be actual clinical trial.

The evaporated milk employed in this investigation came from one pooled batch of milk to insure uniform composition. One portion of the evaporated milk was subjected to three seconds of irradiation by the carbon arc lamp, the evaporated milk flowing in a constant film over the interior of a cylinder in the center of which burned the carbon arc. Another portion of the same milk was canned without irradiation. Assays of the vitamin D content of the irradiated milk performed at the Children's Hospital of Philadelphia showed that there were approximately 125 U.S.P. units* of vitamin D in each 14.5 ounce can of milk. Since all the irradiated milk used came from one pooled batch, the constancy of vitamin D content from can to can was assured. Furthermore, assay of the milk at the beginning and end of the study indicated that there was no appreciable change in the vitamin D content

From the Children's Hospital.

The funds for these studies were furnished by the Wisconsin Alumni Research Foundation.

*Approximately equivalent to 45 Stoenbeck units.

during the four month period covered by the investigation. The evaporated milk which was not subjected to ultraviolet irradiation was used for preliminary feeding as will be described. This nonirradiated milk showed approximately 30 USP units per can.

Twenty-four infants were selected for this study according to the following criteria:

1 Race

The infants were all negroes. They were selected because of their greater susceptibility to rickets.

2 Age

The infants were all under five months of age at the beginning of the study. Table I indicates the age distribution of the infants.

TABLE I

AGE IN WK	NUMBER OF INFANTS
1-4	1 (9 days old)
5-8	10
9-12	4
13-16	4 (1 later withdrawn from study)
19-20	5

The age limit was chosen because it was felt that infants in this age period were growing actively and were highly susceptible to rickets.

3 Sex

Male infants only were chosen. Calcium and phosphorus balance studies were made on all infants in the series (the results of which will be reported later). Male babies were selected because of the greater ease in collection of urine.

4 Health

A Rickets

As far as possible the attempt was made to select infants who were free from rickets. This was not entirely possible, and five had a mild degree of rickets at the beginning of the study.

B Tuberculosis

Physical examinations and Mantoux tests showed freedom from tuberculosis.

C Syphilis

Serologic studies and physical examinations showed that all the infants were nonsyphilitic.

The study was carried out during the winter and spring from Jan 2, 1934, to May 15, 1934, thereby minimizing any slight antirachitic effect of the sunlight coming through the glass windows of the ward in which the infants were kept.

All of the infants were hospitalized during the entire period of the

study We believe that more careful observation of the progress of the infants, more accurate records of actual intake of milk and the better elimination of other factors which might exert an antirachitic effect are assured on the hospital ward than in the out patient clinics Furthermore balance studies of calcium and phosphorus are obviously impossible with out patients

The infants were quartered in one ward in the Children s Hospital of Philadelphia This ward was isolated from the rest of the hospital and each infant was in a separate glass-enclosed cubicle A complete history was taken and a physical examination performed on each infant before he was admitted to the ward Complete blood counts including examination for sickling of the red cells were made on admission and before discharge from the ward A daily record of each infant's weight was kept and measurements of length fontanels and circumference of head chest and abdomen were taken at the beginning and end of the study Roentgenograms were taken of an upper and lower extremity on admission and were repeated at approximately monthly intervals At about the same intervals examinations were made independently by two of us (J S and M R) for clinical evidence of rickets using as major criteria craniotables beading of the ribs, and enlargement of the wrists We adopted an arbitrary clinical scale for these signs, varying from one plus to four plus in each instance one plus being a barely perceptible sign and four plus a very marked one In almost all instances blood was withdrawn for phosphorus and calcium determinations at approximately the same time that the periodic roentgenograms were taken The latter were interpreted by Dr Ralph S Bromer, roentgenologist of the hospital Consultations concerning the roentgenograms were later held with Dr Edwards A Park and Dr Martha Eliot

All of the infants were given nonirradiated milk for a period of about one month at the end of which time they were divided into two groups, one remaining on nonirradiated milk and the other receiving irradiated milk The initial control period served to eliminate the effect of any previous antirachitic therapy and provided as uniform a starting point as possible for the new antirachitic agent under consideration This method of dividing the infants into two groups had a double purpose, namely to test the preventive as well as the curative value of the irradiated milk

The feeding program was uniform for each infant The milk was diluted equally with water and 5 per cent of dark corn syrup was added This mixture was offered to the infants at a level of 55 calories per pound of expected body weight Tomato juice was given as an antiscorbutic agent at a level of 5 cc per pound of expected body weight In addition iron as ferric ammonium citrate was fed 1 per cent being added to the tomato juice We were fully aware of the

fact that iron is usually without effect before the fifth month of life, nevertheless, because some of our infants had reached this age, it was considered best to add it to the dietary of all the infants. It is unlikely that the level of iron administered could have had any influence on the evolution of rickets, as it was far below the levels utilized by Block and Diamond⁴ in producing rickets in rats. Other than water, which was given ad libitum, nothing else was included in the dietary of the infants.

While the incidence of upper and lower respiratory tract infections seemed very large in these infants, the careful daily examinations may account in part for this. Any rise in temperature above 100° F. was usually accounted for by a mild upper respiratory tract infection. Many of these minor infections would certainly be overlooked in the homes from which these infants were taken. However, we do believe that there was a higher incidence of respiratory tract infection in the ward than there would have been in a similar group of infants in a well-baby out-patient clinic. This is in keeping with the experience of others concerning well infants in hospitals.

While the plan of our study differs in several respects from the procedure outlined by Eliot and Powers⁵ for evaluating antirachitic agents clinically, we believe that the test to which we have subjected this milk is as rigid and severe as is possible. The infants were all actively growing negroes, receiving no other antirachitic agent than their milk. They were kept under the constant observation of trained observers. Furthermore, we believe that differences in environment and differences in handling which occur in studies on out-patients introduce variable factors which limit the value of the studies.

RESULTS

On the whole the clinical evidences of rickets were usually in agreement with the roentgenologic evidence. However, in some cases we found a lack of agreement (Table II). Since the clinical signs were recorded independently by two observers and were found to coincide, we believe that the subjective error in our clinical observations has been reduced to a minimum. While the value of enlargement of the costochondral junctions as evidence of rickets may be questioned, craniotabes has usually been accepted as a sign of rickets in the absence of any other known causes of craniotabes, e.g., syphilis. That this is not always true is apparent in Table II, in which are listed five infants who showed definite craniotabes which we are quite certain was not the physiologic craniotabes of infants, and yet there was no roentgenographic evidence of rickets. Jundell⁶ in a study of the clinical significance of craniotabes concluded that it is not necessarily a rachitic phenomenon.

In Table II it will be seen that a clinical diagnosis of rickets in eleven of the twelve infants was made before roentgenographic evidence appeared. Since the consensus is that the roentgenogram is the most trustworthy criterion, in Tables III, IV and V, the diagnosis of rickets rests entirely upon the roentgenographic evidence.

Table III summarizes the course of nine infants (B, D, E, G, J, K, L, Y, Z) who were free from rickets roentgenologically when they were placed upon the irradiated evaporated milk, after having been on the nonirradiated evaporated milk for periods of three to eight and one half weeks. Seven of these infants continued to be free from rickets while two (E, Y) developed rickets which began to heal spontaneously while they were on the same irradiated milk. Clinical signs of rickets

TABLE II

LACK OF AGREEMENT BETWEEN CLINICAL AND ROENTGENOGRAPHIC EVIDENCES OF RICKETS

IN FANT	TIME	CLINICAL SIGNS OF RICKETS			X RAY EVIDENCE OF RICKETS	SUBSEQUENT COURSE OF INFANT
		CRANIO TABLES	BEADING OF RIBS	ENLARGEMENT OF WRISTS		
A	1/ 2/34	0	Moderate	Slight	0	Developed rickets shown by x ray and increase in clinical signs.
D	3/13/34	0	Slight	Questionable	0	Beading increased moderately but x ray never showed rickets.
E	3/13/34	0	Slight	0	0	Developed rickets, evidenced by x ray and increase in clinical signs.
F	1/ 6/34	0	Moderate	Slight	0	Developed rickets, evidenced by x ray and increase in clinical signs.
J	4/ 7/34	Slight	Slight	Slight	0	X ray never showed signs of rickets. Beading increased moderately.
K	3/13/34	0	0	Slight	0	X ray never showed signs of rickets. Developed slight beading which persisted.
Q	1/10/34	0	0	0	Mild rickets	Subsequently developed a mild beading while x ray still showed rickets.
S	1/16/34	Slight	Moderate	Slight	0	Developed exaggeration of his clinical signs along with x ray signs of rickets.
T	1/10/34	Moderate	Moderate	Slight	0	Developed exaggeration of his clinical signs along with x ray signs of rickets.
U	3/ 2/34	Slight	Moderate	0	0	Developed exaggeration of his clinical signs along with x ray signs of rickets.
Y	2/14/34	0	Slight	0	0	Developed rickets by x ray and increase in clinical signs.
Z	4/ 7/34	Slight	Slight	0	0	Never developed x ray signs of rickets. craniotables persisted.

TABLE III
PREVENTIVE EFFECT OF IRRADIATED EVAPORATED MILK

IN- FANT	AGE AT START	WEIGHT AT START	RICKETS AT START	CONDITION AT END OF PERIOD ON NONIRRAD EVAP MILK	GAIN IN WEIGHT ON NONIRRAD MILK EVAL	PERIOD ON IRRADIATED EVAPORATED MILK	GAIN IN WEIGHT ON IRRAD EVAP MILK	GAIN IN LENGTH IN INCHES (4 MO)	RESULT
B	15½ wk	9 lb 12 oz	None	On milk 5 wk No rickets	3 lb 3 oz	On milk 12 wk 12 oz (103 units vit D) daily	2 lb 1 oz	1½	Never had rickets at any time
D	4 wk	9 lb 1 oz	None	On milk 6 wk No rickets	2 lb 7 oz	On milk 11 wk 12½ oz (105 units vit D) daily	3 lb 8 oz	5	Never had rickets at any time
E	7 wk	9 lb	None	On milk 6 wk No rickets	3 lb 7 oz	On milk 12 wk 12 oz (103 units vit D) daily	3 lb 9 oz	4½	Developed a very mild rickets after 8 wk on irr ad evap milk Healed after 4 wk on same milk
G	9 wk	12 lb 13 oz	None	On milk 4½ wk No rickets	2 lb 12 oz	On milk 12 wk 13½ oz (117 units vit D) daily	4 lb 1 oz	3½	Never had rickets at any time
J	6 wk	6 lb 8 oz	None	On milk 4½ wk No rickets	1 lb 12 oz	On milk 12 wk 10 oz (88 units vit D) daily	4 lb 3 oz	5	Never had rickets at any time
L	11½ wk	9 lb 8 oz	None	On milk 3 wk No rickets	1 lb 4 oz	On milk 13 wk 11½ oz (101 units vit D) daily	3 lb 8 oz	3½	Never had rickets at any time
Y	5 wk (twin)	6 lb 13 oz	None	On milk 8 wk No rickets	1 lb 6 oz	On milk 7½ wk 10½ oz (92 units vit D) daily	2 lb 1 oz	3½	Developed a moderate rickets which began to heal spontaneously on the same milk
K	9 days	5 lb 6 oz	None	On milk 8½ wk No rickets	2 lb 6 oz	On milk 6½ wk 10½ oz (90 units vit D) daily	2 lb 4 oz	4½	Never developed rickets at any time
Z	8 wk	8 lb 8 oz	None	On milk 7½ wk No rickets	3 lb 9 oz	On milk 4½ wk 14½ oz (127 units vit D) daily	2 lb 7 oz	5½	Never developed rickets at any time

were present in both infants in the absence of roentgenographic bone changes at the time they began taking irradiated milk. In these two infants who developed rickets, we have been unable to correlate this with any differences in rate of growth or level of vitamin D intake as reported by Wilson.⁷

Table IV shows the course of thirteen infants who had developed varying degrees of rickets while on nonirradiated evaporated milk and who were placed on the irradiated evaporated milk to test its curative value. Two infants showed almost complete healing. Three infants showed slight healing. In two infants there was an advance of the rachitic process before slight healing set in. In four infants there was no healing, and in two there was continued advance of the rickets. One of these two latter infants showed no healing after ten daily doses of 15 cc of cod liver oil. Again we were not able to correlate any change in the rachitic process in any of these infants with definite changes in growth or level of vitamin D intake.

One infant (C) whose course is summarized in Table V did not develop rickets after a twelve week period of consumption of non irradiated milk. While it could be argued that this infant failed to gain much weight we know that he was not malnourished at the end of this period but instead grew from a short stocky infant into a long slender one. Moreover some of the infants developed rickets during a period when they grew very little. In fact Infant N developed rickets over a period during which he lost weight.

One infant (W) because of repeated illnesses necessitating therapeutic procedure which confused any interpretations of his clinical data, has been omitted from consideration.

The blood calcium and phosphorus determinations will be considered in detail in a presentation of the calcium and phosphorus balance studies. They were in approximate agreement with the roentgenographic and the clinical findings.

It was of interest that the administration of iron as mentioned affected favorably the hemoglobin level and the red cell count in only two of the twenty three infants. One infant (W) whom we have omitted from consideration as far as the rickets was concerned because of illness, showed an increase of 10 per cent in the hemoglobin level while the red cell count remained the same. One infant showed evidence of sickling of the red cells without the accompaniment of clinical symptoms which corresponds to the usual incidence in the Negro race.

DISCUSSION

From the evidence presented in Table III irradiated evaporated milk containing 125 U.S.P. units of vitamin D per 145 ounce can appeared to be an adequate agent for the prevention of rickets in infants.

TABLE IV
CURATIVE EFFECT OF IRRADIATED EVAPORATED MILK

IN- FANT	AGE AT START	WEIGHT ON ADMISSION	RICKETS ON ADMISSION	RICKETS AT END OF PERIOD OF NON-IRRADIATED EVAPORATED MILK	GAIN IN WEIGHT ON NON-IRRADIATED EVAP MILK	PERIOD ON IRRADIATED EVAPORATED MILK	GAIN IN WEIGHT ON IRRADIATED EVAP MILK	GAIN IN LENGTH IN INCHES (4 MO.)	RESULT
A	8 wk	10 lb 5 oz	None	On milk 12 wk Moderate rickets	3 lb 1 oz	On milk 5½ wk 13 oz (112 units vit D) daily	1 lb 9 oz	3½	Rickets progressed while on irradiated evaporated milk
F	20 wk	17 lb	None	On milk 8 wk Mild rickets	2 lb 2 oz	On milk 8 wk 15 oz (129 units vit D) daily	8 oz	1	Good healing at end of time
H	20 wk	14 lb 12 oz	Mild rickets	On milk 4 wk Moderate rickets	1 lb 6 oz	On milk 11½ wk 10½ oz (90 units vit D) daily	Lost 2 oz	3	Rickets advanced at first then began to heal
M	8 wk	9 lb 1 oz	Very mild rickets	On milk 7 wk Marked rickets	2 lb 7 oz	On milk 8½ wk 13½ oz (114 units vit D) daily	1 lb 13 oz	4	Rickets stationary—no healing Cod liver oil —15 cc daily for 10 days had no effect Beginning healing at end of period
N	15 wk	16 lb 11 oz	None	On milk 7½ wk Moderate rickets	Lost 3 oz	On milk 5 wk 12½ oz (108 units vit D) daily	1 lb 4 oz	2	Rickets stationary—no healing
O	9 wk	13 lb 8 oz	None	On milk 8 wk Mild rickets	3 lb 3 oz	On milk 7 wk 14½ oz (125 units vit D) daily	2 lb 11 oz	3	Rickets stationary—no healing
P	16½ wk	11 lb 6 oz	Mild rickets	On milk 5 wk Moderate rickets	7 oz	On milk 10 wk 12½ oz (108 units vit D) daily	2 lb 11 oz	3	Rickets completely healed
Q	7 wk	10 lb	Very mild rickets	On milk 6½ wk Mild rickets with tetany	1 lb	On milk 9 wk 10½ oz (90 units vit D) daily	1 lb 10 oz	1½	Tetany controlled by milk Slight healing of rickets
R	13½ wk	13 lb 2 oz	None	On milk 10 wk Moderate rickets	2 lb 3 oz	On milk 4½ wk 10½ oz (90 units vit D) daily	Lost 10 oz	2½	Rickets stationary—no healing

TABLE IV—CONT'D

IN PANT	AGE AT START	WEIGHT ON ADMISSION	RICKETS ON ADMIS- SION	RICKETS AT END OF PERIOD OF NONIRRADIATED EVAPORATED MILK	GAIN IN WEIGHT ON NONIRRADIATED EVAP MILK	PERIOD ON IRRADIATED EVAPORATED MILK	GAIN IN WEIGHT ON IRRAD. EVAP MILK	GAIN IN LENGTH IN INCHES (4 MO.)	RESULT
S	9½ wk.	12 lb	None	On milk 3 wk. Very mild rickets.	1 lb	On milk 12 wk. Took 11½ oz. (90 units vit D) daily	~ lb 2 oz.	1	Rickets advanced slightly then good healing set in.
T	14 wk.	8 lb 7 oz.	None	On milk 7½ wk. Moderate rickets.	1 lb 14 oz.	On milk 8 wk. Took 10½ oz. (90 units vit D) daily	1 lb 3 oz.	2	Rickets advanced slightly
U	4½ wk.	8 lb 1. oz.	None	On milk 10 wk. Mild rickets.	3 lb 5 oz.	On milk 6 wk. Took 11 oz. (94 units vit. D) daily	11 oz	3½	Beginning healing at end of time.
V	5 wk (twin)	7 lb 12 oz.	None	On milk 10 wk Marked rickets.	2 lb 10 oz.	On milk 6 wk. Took 10½ oz. (92 units vit. D) daily	1 lb 2 oz	3½	Rickets stationary—no healing

TABLE V

INFANT FREE FROM RICKETS AFTER TWELVE WEEKS ON NONIRRADIATED EVAPORATED MILK

IN PANT	AGE	WEIGHT AT START	RICKETS AT START	PERIOD ON NON IRRAD EVAP MILK	GAIN IN WEIGHT ON NONIRRAD EVAP MILK	PERIOD ON IRRADIATED EVAPORATED MILK	GAIN IN WEIGHT ON IRRAD. EVAP MILK	GAIN IN LENGTH IN INCHES (4 MO.)	RESULT
C	18½ wk.	13 lb 8 oz.	None	On milk 1 wk. No rickets.	1 lb	On milk 4 wk. Took 10½ oz. (90 units vit D) daily	8 oz.	3½	Never had rickets. Crew from small stocky in fant to long slender one Not malnourished

It should also be noted that two of the infants in this group who showed no roentgenologic evidence of rickets at the time they were put on irradiated milk developed mild roentgenologic evidence of rickets after the change. These signs disappeared rapidly while they continued to receive the same irradiated milk.

While the results in these two infants might be considered as evidence for the curative rather than prophylactic value of the irradiated evaporated milk they were included in the above group, because of the criteria used for the diagnosis of rickets, i.e., they were free from rickets by roentgenologic examination at the time of the change from nonirradiated to irradiated milk.

From the evidence presented in Table IV, irradiated evaporated milk containing 125 U.S.P. units of vitamin D per 14.5 ounce can appears to be unreliable for the cure of rickets in infants. Although there were two infants who showed complete healing, three infants slight healing, and two infants an advance in the rachitic process followed by slight healing, nevertheless, there were four infants who showed no healing, and two infants in whom the rachitic process actually advanced without healing. It is possible that the last two infants fall in that group which is refractory to antirachitic therapy since one of them gave no evidence of healing even after ten days of therapy with 15 c.c. of cod liver oil daily.

Our data do not warrant any conclusions concerning the relationship between the severity of the rachitic process, the rate of growth in length and weight, and the amount of antirachitic agent administered, as noted by Wilson.⁷

Also, from these studies no conclusions could be drawn as to the variation in antirachitic value for infants of different antirachitic agents containing an equivalent number of vitamin D units by rat assay. The interesting studies of Waddell⁸ appear to throw some light on this question.

SUMMARY

A study is recorded of the antirachitic value of irradiated evaporated milk, containing 125 U.S.P. units of vitamin D per 14.5 ounce can, in twenty-three male negro infants. This milk appeared to be an adequate agent for the prevention of rickets in negro infants. It also appeared to be an unreliable agent for the cure of rickets in negro infants.

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OBSERVATIONS ON POSTURAL TREATMENT OF UPPER RESPIRATORY INFECTION

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UPPER respiratory infection forms a constant and important problem in general medical practice just as it does in otolaryngology. This is especially true because one must deal not only with local infection in the nose and sinuses but also with complications in the ears, throat, chest, and gastrointestinal tract.

Both general and local measures are employed to combat such infection. In regard to general measures in treatment I need make no comment save that recent years have brought changes in ideas and methods due to better understanding of physiology in health and in disease. A basis of scientific facts must always replace tradition and empiricism.

Considerable advance too, has been made in our understanding of the nose and sinuses. Here physiology is concerned with the ciliated mucosa that forms the lining and functioning structure of these cavities. Much has been learned of the reaction or response of this mucosa to disease and also to the various substances so commonly used in the nose for the purpose of treatment.

Normal physiologic activity in the nose and sinuses to the extent that it concerns us here consists of constant ciliary sweeping plus the steady outpouring of sufficient serous and mucoid fluid to keep moist the surface in which the cilia beat and to humidify the inspired air. All ciliary sweeping within the sinus is toward the ostium; all nasal sweeping is toward the pharynx. The final destination of all ciliary drainage is the mouth of the esophagus where it is swallowed.¹

Ciliary flow is at the rate of one half a centimeter per minute requiring about five minutes to pass from the anterior to posterior parts of the nasal chambers. This constitutes the chief cleansing and defense mechanism of the upper respiratory tract normally and probably in disease as well. Other defense factors are present such as phagocytic cells in small number which wander throughout the mucosa and antibodies in varying strength. The secretions are very slightly antiseptic due to the presence of lysozyme.

At the onset of infection defense is concerned with keeping up the ciliary cleansing, pouring out additional mucus, and mobilizing phagocytes and antibodies. These processes are more or less disturbed and

impeded by the bacterial toxins, and there is an initial sharp decrease in the effectiveness of lysozyme.²

The earliest sweepings of toxins and bacteria down the pharynx and toward the esophagus are of course the most toxic due to temporary lack of antibodies. Hence the early sore throat, laryngitis, malaise, and other symptoms.

When early resolution fails to take place, the infection progresses with more local discomfort and more disturbance of function. Nasal congestion occurs, and there is outpouring of mucopus in reaction to bacterial invasion of the mucosa. Congestion, overload of secretions, and prolonged contact with toxins impair ciliary activity, and further interference comes from drying of purulent films. Large areas of cilia may become paralyzed, allowing accumulations of mucopus. Sinus drainage is further impaired because blockage of the meatus cuts off the essential stimulation to ciliary activity that comes from the plus and minus alternation of air pressure during respiration.³ Perhaps the worst interference is from diving, which paralyzes all affected cilia.⁴

Local treatment during a nasal infection can be of direct aid to some functions of the mucosa and of indirect aid to others. To be logical and effective it must tend toward removal of factors interrupting ciliary and other mucosal activities.

Shrinkage of the mucosa relieves congestion and restores the action from alternating air pressure. This alone goes far toward restoration of function. Emptying the nasal chambers of retained secretions and moistening the epithelium give further aid, as does also any actual stimulation of ciliary function.

How to accomplish these things with the least trauma, physical and chemical, is the essential problem. For it is obvious that to whatever extent a drug or method is harmful it counteracts whatever good it does.

Local measures commonly employed in treatment constitute a wide variety. Some physicians use tampons of silver protein, others employ drops of various substances usually oily, applied with the head tilted back, others depend on sprays, or irrigations, or antrum washings, or simply throat swabbings with argyrol or mercurochrome. These procedures were devised at a time when nasal physiology was not so well understood as it is today.

Concerning the various drugs commonly used for treatment of the nose, recent experimental work by Lierle and Moore⁵ and Proetz⁶ is of prime interest. By using fresh ciliated epithelium from the human nose, the effect of drugs was studied at close range. These investigations although independently made were in striking agreement.

Physiologic salt solution appears to have no effect on ciliated membrane either for better or for worse. Tissue immersed in it for two

hours still functions. This is explained by similarity to the normal fluids of the nose

Ephedrine, 0.5 to 3 per cent, in normal salt solution is also harmless. One investigator reported even sustained acceleration of ciliary activity in eleven of twenty tests.

With all other drugs and fluids used we read a different story. Tap and distilled water and concentrated salt water are decidedly harmful as they quickly stop all ciliary activity. Mild silver protein (argyrol neosilvol) causes definite slowing of ciliary activity. The slowing is explained as due to plain water solvent, which has to be used with these drugs, and also to precipitation or clumping of the drug over the surface. Cocaine in more than 2.5 per cent strength quickly causes slowing or paralysis of the cilia. Adrenalin, in a dilution of 1:1000 causes immediate paralysis of the cilia, while a dilution of 1:5,000 causes slowing. Eucalyptol, menthol, thymol, zinc sulphate and mercurochrome are all definitely harmful to ciliary activity. Menthinolate in dilutions up to 1:10,000 causes slowing of cilia. Mineral oil causes marked slowing of the ciliary stream, not so much by direct action on the cilia as from lymph, as a heavy inert blanket on the surface.

From all this we learn that ephedrine in normal salt solution stands out as the one preparation that we may use in the nose with apparently no harmful effect as regards physiologic function. It may even accelerate the ciliary beat. Also we know that ephedrine applied to mucous membrane contracts the capillaries and effectively reduces swelling and hyperemia, effects which are so desirable in infection.

It is apparent furthermore that most of the drugs commonly used in the nose do not produce the effect the physician intends. On the contrary they cause interference with vital defense processes something he decidedly does not intend. For to slow or paralyze ciliary activity is to break down our most potent defense factor and to lend aid to the forces of infection. The recognition of nasal physiologic function no longer allows us to believe complacently that oil is harmless or that colloids are soothing or still less that mercurochrome in the throat cures infection that is in the nose.

Having in ephedrine, an acceptable drug we need also a method of treatment based on the peculiar anatomy of the nose and sinuses. If we are open minded we must soon come to feel kindly disposed toward the use of the head low posture. For only by posture can we hope to reach so irregular and intricate a labyrinth of spaces and structures.

Such use was recommended by Proetz,¹ of St. Louis, and the technique described by him has been in limited use for eight years. In the Proetz technic the patient lies on his back with his head hyperextended over the end of a table or cot to an inverted position. Treatment fluid is then instilled in the nostrils and gravitates to the superior nasal areas which are now dependent. It is thus intended to come in contact with and

bathe the upper meatuses and turbinates. Bear in mind that the sinus ostia are all in the upper half of the nose, and the sinuses are all involved to some extent in all colds.

However, there are several objections to the Proetz technique if considered as a possible routine procedure. First, it is designed to reach the sphenoid and posterior ethmoid area rather than to give equal distribution throughout the upper nose. This is inherent in this posture for it is difficult to get the patient's head sufficiently upside down. This causes the treatment fluid to miss the antrum and anterior ethmoid regions, which are very important. Second, this posture is often very uncomfortable and moreover, its strangeness tends to frighten children and to make them uncooperative. Third, on recovering from the Proetz position, the patient is usually unable to prevent the fluid nasal contents from pouring backward into the pharynx and mouth.

Nevertheless, it is believed that this concept marked a long step for-

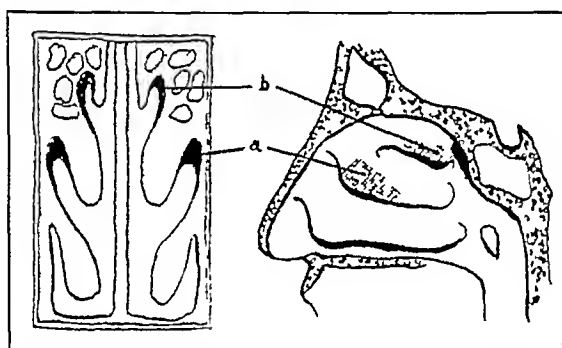


Fig 1—Schematic drawings of A cross-section of nasal cavity and B lateral nasal wall. The sinus ostia are grouped in two areas as indicated: a, the anterior group (maxillary, frontal and anterior ethmoid); b, the posterior group (sphenoid and posterior ethmoid).

ward in the direction of rational nasal therapy. It is fully realized that such things as posture and gravity normally are not factors in nasal and sinus damage, but we are dealing here with congestion and purulent discharge, which are not normal findings and are often associated with marked abnormality of function as a result of disease.

A much simpler position for postural treatment has been found where the drawbacks mentioned are avoided. The desirable posture, of course, is with the head so inverted that the roof of the nasal chambers is at all times level or horizontal in the anteroposterior plane. Fluid instilled in the nose then would become equally distributed throughout the superior nasal areas and would bathe all regions where sinus ostia are found. To be practicable, the position must allow the patient to be sufficiently comfortable to retain the posture with ease for several minutes.

With the patient placed on his side and the lower shoulder somewhat elevated we can by bending the head downward laterally obtain a posture that approaches the ideal rather closely. A full description of this procedure was published a year and a half ago.⁸

With but little care this position is easily attained and can be held with relative comfort for as many minutes as desired. This is especially true of children because of their flexibility. As it is not too far removed from the side position in sleep the element of fear is almost never present. A fact of prime importance is that while it is desirable to place the head in as nearly an upside-down position as possible full inversion is not here essential. This is because in the side or lateral position the roof of the nasal fossae is at all times level in the anteroposterior plane and is dependent just as soon as the head is bent below the horizontal.

The first step in treatment is to have the nose well opened by the use of an ephedrine spray or by topical application of ephedrine or

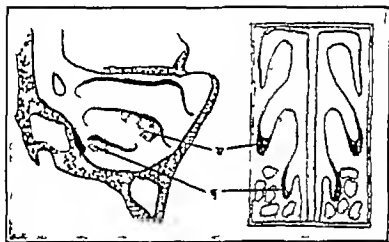


Fig. 2.—Same drawings inverted to illustrate the principle of posture in treatment. It will be seen how readily the upper meatuses and sinus ostia may be reached in this position by fluid instilled in the nose.

very dilute cocaine. Then with the patient in the lateral head low posture the treatment fluid is instilled in the nostrils and flows by gravity to the now dependent superior nasal areas. For this purpose 1 per cent ephedrine in physiologic salt solution has been found satisfactory. The solution is first warmed to approximately body temperature.

The solution is left in for from three to five minutes. During this time the patient should breathe through the mouth. At termination of treatment the head is rotated to the position of face-down. This allows the fluid contents of the nose to run out of the nostrils and is assisted by gentle nose blowing. Since nasal contents need at no time enter the pharynx, there should be no annoyance from taste of the ephedrine, and none need be swallowed.

If, as part of the treatment, one wishes to have some of the ephedrine solution actually enter the sinuses one may accomplish this by suction displacement.⁹ From its known action ephedrine within a sinus will prolong the effect of treatment and will favorably affect drainage by

reducing congestion and stimulating ciliary action. In acute conditions this has seemed unnecessary, but in cases in which the infection is subacute it has seemed distinctly useful, especially in children. In stubborn cases I have resorted to displacement many times with apparently favorable effect.

In practice the use of this method of postural treatment serves well as a routine procedure in the care of sinusitis and so-called bad colds.



Fig 3—Side view of child in lateral head-low position. More nearly complete inversion may easily be obtained as a rule but is not essential. This posture is reasonably comfortable.



Fig 4—End view of same posture. It is seen that the roof of the nasal fossae is approximately level in the anteroposterior plane; this is the essential thing as it insures equal distribution of the treatment fluid throughout the upper nasal areas.

This applies to both adults and children. It entails practically no discomfort. Since it does not traumatize the mucosa either physically or chemically, there is no local reaction. The procedure is easily carried out and requires no special equipment. It can be applied in any office and in any home. It can be repeated as often as desired. It requires a little more time and attention than is usually given these cases, but results fully justify this. Between treatments patients who are old enough can assist by the use of a spray of 1 per cent ephedrine.



Fig. 5.—Radiograph showing presence of lipiodol in all sinuses of both sides. Patient, an adult, was placed in the lateral head low position and iodized oil instilled in both sides; this was followed by suction displacement. It illustrates the contact of the fluid used with all the sinus ostia.



Fig. 6.—Same as Fig. lateral view

Not only have results been good, but also certain desirable changes in the routine care of patients have been made possible. Thus the use of tampons and other similar procedures requiring intranasal instrumentation have been discarded. Postural treatment is more effective and at the same time is much cleaner and avoids all trauma to the ciliated mucosa. The common use of so called nose drops, with home-use instructions to instill in the nose with the head tilted back has nothing to recommend it. Nothing could be more futile. Fluid thus used can do no more than run directly backward into the throat and can reach no higher than the dependent border of the lower turbinate. Ephedrine used in this way will produce only general symptoms from being swallowed, without local benefit. With the use of postural treatment, therapeutic antrum lavage is but rarely necessary. Postural treatment appears to give adequate drainage, it reaches both antrums at once, and it has the added advantage of reaching also the associated ethmoid cells that are so commonly involved with the antrum. Surgical antrum windows become necessary less often than formerly. One feels as if he has a means of greater control over these cases and hence can often avoid surgical procedures that would otherwise have seemed indicated.

It is frankly stated, however, that postural treatment has not been found of permanent beneficial effect in all long-standing cases. It does bring needed temporary relief from congestion and blockage. It does not supplant proper surgical intervention in cases in which permanent and constant relief is required, although this type of case appears to become less common. Its use in allergic nasal conditions is only palliative.

SUMMARY AND CONCLUSIONS

The most important physiologic activity of nasal and sinus mucosa, in regard to infection, is ciliary sweeping.

The purpose of all nasal treatment is to relieve the ciliated mucosa of a pathologic load of congestion and secretions and promote its ability to carry on more efficiently. Ephedrine in normal salt solution has been shown to be the drug of choice for this purpose, it is entirely harmless to ciliary activity, and it effectively reduces mucosal congestion and restores physiologic function.

The use of the lateral head-low posture is believed to be the rational method of applying treatment because it is based on anatomic and physiologic principles peculiar to the upper respiratory tract.

Those of us who have used this plan of treatment have obtained distinctly favorable results in the control of colds and acute and subacute sinusitis.

The prevention of undue progress in every cold is important, not only for present health, but also in the prevention of complications and chronic infection with their added difficulties.

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1904 FRANKLIN STREET

CONGENITAL RHABDOMYOMA OF THE HEART ASSOCIATED WITH ARRHYTHMIA

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IN 1931 Farber¹ contributed a very complete review of the known cases of cardiac rhabdomyoma, at that time totaling forty-one. He emphasized the frequent association of this type of tumor with tuberous sclerosis of the brain and embryonal cysts of the kidney. Since his report two other cases of rhabdomyoma have appeared in the literature. Yater,² in a series of cardiac tumors, had one case of rhabdomyoma occurring in a colored child five years old who came into the hospital because of convulsions. The heart at necropsy contained two subendocardial nodules of tumor tissue, one of which was in the interventricular septum very close to, but not invading, the left bundle branch. The child also had tuberous sclerosis of the brain and renal cysts. Reitano and Nucciotti³ presented the case of an infant who was intensely cyanotic and died in the first day of life, at necropsy was found an enormous tumor of the heart, which was thought to be a rhabdomyoma. It had multiple seats of origin, and the writers believed that it originated from the primordial undifferentiated cardiac cells. There were no abnormalities in any other organ.

It has been a matter for conjecture, as is mentioned by Farber, that in no instance has abnormal cardiac rhythm been part of the clinical picture of this condition, despite the fact that the tumor has usually been widespread. Indeed, many writers have supported the theory that the tumor arises from the Purkinje cells of the conduction system because of the similarity between the two types of cells. At present, however, the preferred theory is that the tumor arises from the primordial cells before they are differentiated.

The following case is reported because it seems to represent the first occasion that cardiac irregularity has been noted in this disease. The irregularity was the outstanding clinical finding and the reason for which the child was referred to the hospital.

M. A. M., a ten month old Italian female, was brought to the New Haven Hospital by her parents on Dec. 10, 1933, at 2:30 P. M., because of tachycardia which was discovered by her physician, Dr. W. C. McGuire, of New Haven.

The family history was not significant, the patient was the only child, and the parents were young, healthy individuals.

From the Departments of Pediatrics and Pathology, Yale University School of Medicine, and the Pediatric Service of the New Haven Hospital and Dispensary.

The birth and neonatal histories were negative. At the age of one month the child was seen in the well baby clinic and was noted to be poorly nourished (weight 6 pounds 10 ounces). Subsequent visits were made only for minor feeding difficulties, but different observers felt that progress was not entirely satisfactory although no definite abnormalities were noted.

Except for colds there were no illnesses until at the age of seven months when the patient suddenly had a convulsion lasting ten minutes and consisting of stiffening and cyanosis. A physician who was called found no obvious cause for this. At the next visit to the clinic the fontanel was found to be closed and the head was thought to be small. The baby was very fidgety, and the note in the record at this time contained a warning to 'watch for neurologic phenomena.

Nothing untoward happened for the next month, but the mother then became afraid that the child was developing rickets and took her to a physician who increased the cod liver oil from two to six teaspoons daily. During the following month that preceding admission the parents observed that the baby experienced sudden transitory periods of pallor.

Two days before admission the patient seemed ill, was irritable, and vomited several times. The physician was called again and as physical examination was negative thought the vomiting might be due to an excess of cod liver oil and ordered the latter reduced. The next day the baby seemed better but the pallor was observed again.

At 2:00 A.M. on the day of admission the mother was awakened by a cry from the child's room and found her extremely pale and looking as though she were going to have a convulsion. She improved after a warm bath and an enema and slept through the night. After her morning milk she vomited and again became pale, remaining so until the physician was called at noon. Examination disclosed a very rapid heart rate in addition to the pallor which was marked and she was referred to the New Haven Hospital.

On admission the temperature was 37.9 C., and respirations, 23 per minute. The color was good neither pallor nor cyanosis being present. (The parents commented on the change from a half hour previously.) Positive findings were limited to the heart which was not enlarged to percussion. The sounds were of tic-tac quality and the rate too rapid to be counted, estimates ranging from 200 to 300. The rhythm was irregular and consisted according to one observer of rapid regular beats in periods of varying length, interspersed with short periods of apparently complete stoppage. Another observer thought the intervening periods were not due to cessation but rather to slowing of the beats. The periods of rapid regular rhythm varied from a few seconds to several minutes. Pressure on the carotid sheaths produced slowing and greater irregularity but release was followed by prompt return to the former state.

Laboratory Data—R.B.C., 5.0 hemoglobin, 97 per cent (Sahli) W.B.C., 20,000 polymorphonuclear leucocytes, 53 per cent lymphocytes 40 per cent monocytes, 7 per cent smear negative. Urine albumin, one-plus acetone, two-plus. Body weight 70.0 gm. Head circumference occipitofrontal, 42 cm. (average for this age is 43 to 44 cm.) Chest circumference 42 in. Length 1 cm.

Fluoroscopy Report—There was rapid, shallow pulsation of both auricles with a regular rhythm. Ventricular pulsations were shallow with a markedly irregular rhythm. There was no constancy in the time relation of the irregularity. Sudden diminution in the rapid beating of the auricular chambers followed compression of the carotid sheath.

Telerontgenogram.—The heart shadow is within normal limits. The lung fields show slightly increased markings.

Electrocardiogram—(Five hours after admission) (Fig 1) The rhythm is regular and the rate, 240. The configuration is consistent with a diagnosis of either tachycardia or auricular flutter with 1:1 rhythm. In view of the reaction to vagus pressure the latter is more likely. Unfortunately no periods of irregularity are included in the tracing.

It was decided to digitalize the patient, and one-quarter of her calculated dose (40 mg per kilogram), 80 mg, was given subcutaneously at 8:00 P.M. in the form of digitofoline. No change was observed for the next three hours and at 11:00 P.M. she received another 80 mg. Almost immediately thereafter the heart was found to have slowed up and to have become more irregular. Her color and general appearance were still good, and in about five minutes the rate picked up again. A half hour later a nurse who was in the room saw the child turn blue suddenly and start to gasp. The intern arrived within the minute and was unable to detect any

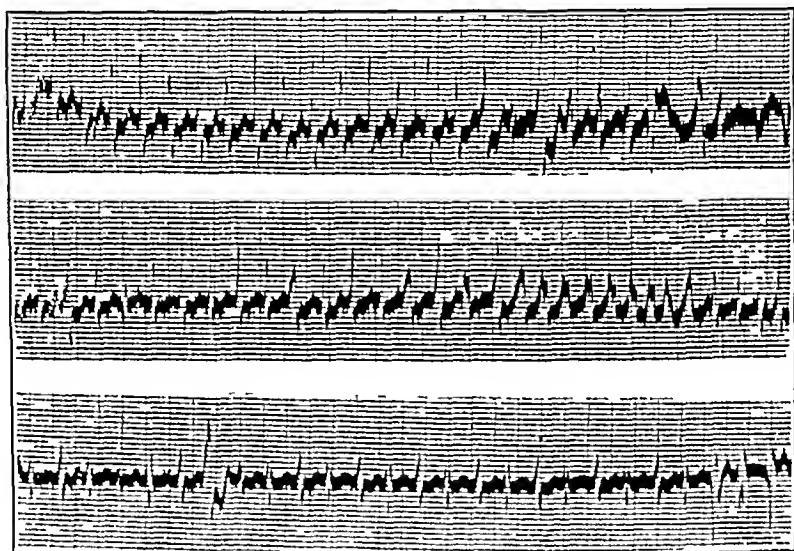


Fig 1—Electrocardiogram

heartbeat although gasping respirations continued for another minute or two. Caffeine and adrenalin, the latter intracardially, failed to have any effect.

The clinical diagnosis was auricular flutter, presumably on the basis of some congenital anomaly.

NECROPSY FINDINGS

The body was very well developed and well nourished. There was no subcutaneous edema. The lips were slightly cyanotic. There were 75 cc of blood tinged fluid in the right pleural cavity and 40 cc of a similar fluid in the left pleural cavity.

The findings of interest were confined to the heart and kidneys.

Heart—The heart weighed 51 gm. The epicardium was intact, smooth, and glistening. The subepicardial fat was scanty. Externally, the red brown myocardium was a mottled yellow in many zones, especially along the course of the coronary vessels. The tricuspid valve had a row of small (1 to 3 mm in diameter), raised, light yellow, fairly firm nodules along its line of insertion (Fig 2). The endocardial surfaces of the right ventricle were smooth and glistening, but the mus-

culature of the columnae carneae and papillary muscles had a light yellow mottled appearance similar to that observed on the external surfaces only more marked and more extensive. This was most noticeable in the musculature of the interventricular septum. At the base of the papillary muscle of the medial cusp of the tricuspid valve, there was a nodular thickening 2 cm. in diameter which extended in to involve the interventricular septum. The anterior cusp of the mitral valve had a large round smooth nodule 2 cm. in diameter located at the point of insertion

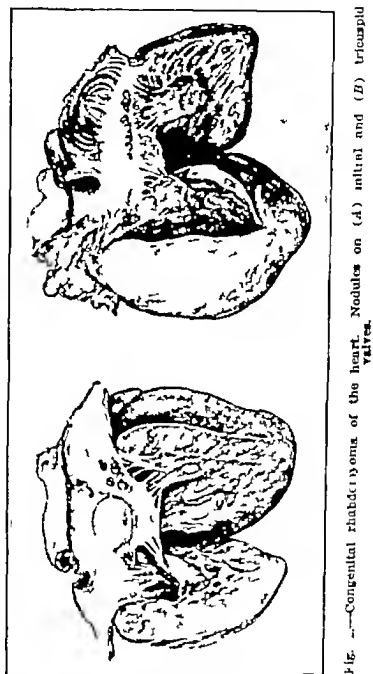


Fig. 2.—Congenital rhabdomyoma of the heart. Nodules on (A) mitral and (B) tricuspid valves.

(Fig. 2) Its external and cut surfaces were light pink yellow and moderately firm. There were four smaller nodules from 2 to 5 mm. in diameter on the valve cusp. The endocardial surfaces of the left ventricle had a mottled light yellow color similar to the right ventricle. The mottled yellow color extended about half way through the ventricle from the endocardial surface. The columnae carneae of both ventricles were rounded and their interspaces were deep and close together. The pulmonary and aortic valve leaflets were thin delicate and not unusual.

Microscopic examination of the heart showed the mottled yellow tissue observed in the gross in the myocardium of both the right and left ventricles to be represented by a neoplasm. There was a rather thin layer of tumor tissue just beneath

the epicardium. Most of the growth lay in the inner portions of the myocardium, a considerable amount being present in the papillary muscles. It invaded the myocardium diffusely and had very irregular and poorly demarcated borders. The nodules on the tricuspid and mitral valves consisted entirely of the same tumor



Fig 3—Tumor cells (below) with adjacent normal myocardium (above)

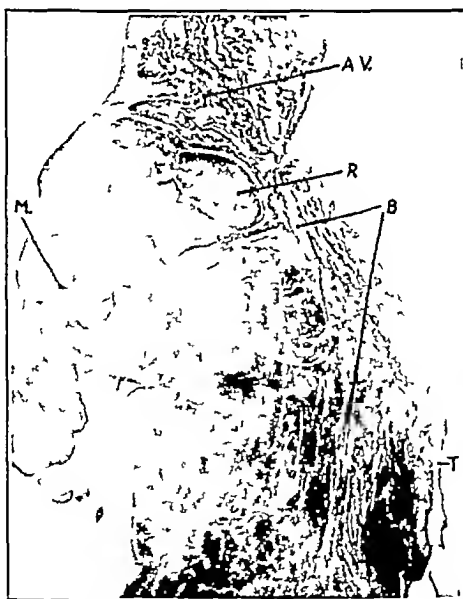


Fig 4—Site of conduction bundle. *M*, mitral valve. *T*, tricuspid valve. *A V*, atrioventricular septum. *B*, blood vessels at site of conduction bundle. *J*, tumor nodule.

The tumor cells had a rather close resemblance to myocardial cells in their general appearance (Fig 3), however, they were somewhat larger and stained light purple in distinction to the light red of the myocardium. Their arrangement was disorderly. They were more or less polygonal in outline and did not tend to be elongated like

myocardial cells, varying considerably in size and shape. Mitotic figures were not seen. The cytoplasm of the tumor cells was finely vacuolated. This vacuolization was fairly marked in some cells so that the cytoplasm appeared in rather fine, radiating strands, giving the appearance described in the literature as characteristic of rhabdomyoma.¹ This vacuolization was apparently not as marked in the cells of this case as in those of the case described by Farber. The nuclei of the tumor cells tended to be large. There was about as much stroma associated with the tumor tissue as with the normal myocardium. The architecture of the myocardium was quite distorted by zones of tumor tissue but was otherwise not especially unusual. Microscopic preparations of the myocardium were stained with phosphotungstic acid and with hematoxylin eosin and by the Mallory aniline blue and the van Gieson methods. Striations were not distinguished in the rhabdomyoma cells.

Serial sections were prepared of the conduction bundle. Each preparation contained interauricular and interventricular septums with parts of the tricuspid and mitral valves attached. The latter valve was partly replaced by a large tumor nodule, and tumor tissue almost completely replaced the myocardium in these preparations. The conduction bundle itself could not be identified but its site in the auriculoventricular connective tissue septum was distinguished by the fact that several arterioles and venules were seen to pass through the septum and to come to lie on the side of the right ventricle (Fig 4). This region, which represented the site of the conduction bundle was completely invaded by tumor.

Kidneys.—The kidneys contained numerous small cysts which were from 2 to 3 mm. in diameter and were filled with clear fluid. These cysts were scattered through the cortex and were best seen on the external surfaces. On microscopic examination they were seen to have a thick wall of connective tissue which was lined in most instances by a well preserved, single layer of flattened epithelial cells.

Brain.—The cerebral findings were confined to minor architectural malformations in the cellular structures of the basal ganglions and the cerebellar cortex. There was no evidence of tuberous sclerosis.

Lungs.—There were numerous extravasations of blood beneath the pleura and into the pulmonary tissue.

DISCUSSION

Classification of the type of arrhythmia which occurred in this case is not easy. The irregularity observed clinically coupled with the electrocardiographic tracing would indicate auricular flutter with varying degrees of block as the most likely diagnosis. The episodes of pallor noted before admission might easily have been due to transient complete heart block.

Cases of disturbance of the heart rate in young children are not rare and similar difficulty has been experienced in identifying the arrhythmia.² Various etiologic conditions for such disturbances have been recognized and probably the most frequent cause has been congenital heart disease. It would appear from this case that tumor of the heart must also be considered in the differential diagnosis of abnormal rhythm in infants.

The clinical aspects of many of the cases of rhabdomyoma have been confined to the cerebral symptoms associated with the accompanying tuberous sclerosis. Cardiac findings, when present have been those of congestive failure. In the present instance the tumor was found

not only invading the cardiac musculature but completely obliterating the auriculoventricular bundle. This is apparently the first time that invasion of the conduction system has been demonstrated. It seems more surprising that there was so little cardiac difficulty rather than that there was any.

Whether the digitalis had any effect on the early death of the patient is problematical. The extensive involvement of the heart at necropsy and the fact that signs of cardiac disorder had appeared so recently and seemed to be increasing in severity would imply that the disease ran its natural course. However, while the dosage of the drug was far below the usual toxic range, the amount given, in a heart so seriously damaged, might have caused it to stop beating.

SUMMARY

A case of rhabdomyoma of the heart in a ten-month-old girl is reported. The most important clinical finding was a cardiac arrhythmia thought to be auricular flutter. At necropsy the tumor was found to invade the conduction system. Congenital cysts of the kidneys were also present.

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A STUDY OF THE SEASONAL INCIDENCE IN THE MORBIDITY AND MORTALITY OF TWENTY THOUSAND BREAST AND ARTIFICIALLY FED INFANTS FOR THE FIRST NINE MONTHS OF LIFE

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THE present paper is concerned with the seasonal incidence of disease among the same group of children referred to in an earlier communication¹ Since these statistics covered a period of five years it is not likely that the seasonal incidence of disease is to be much affected by differences in the type of infection which may occur, especially respiratory infection.

In the study of morbidity, any note on the chart that indicated any feeding disturbance, cold or respiratory infection, or other infection is classified as an infection These were divided into three main groups respiratory infections, gastrointestinal and unclassified

In Tables I and II and Charts 1 2 3, 4 5 and 6 the months are given seasonally as follows March April, and May as spring June

TABLE I
SEASONAL MORBIDITY

		SPRING MAR. APR. MAY	SUMMER JUNE, JULY AUG	FALL SEPT OCT NOV	WINTER DEC JAN FEB
<i>Breast Fed</i>					
Respiratory	No	799	811	698	929
	Per cent	9.1 %	9.3 %	7.1 %	9.5 %
Gastrointestinal	No	70	103	171	70
	Per cent	0.7 %	1.0 %	1.7 %	0.7 %
Unclassified	No	77	100	77	93
	Per cent	0.7 %	1.1 %	0.7 %	0.7 %
<i>Partially Breast Fed</i>					
Respiratory	No	877	410	614	1024
	Per cent	10.2 %	4.7 %	7.1 %	11.7 %
Gastrointestinal	No	163	517	265	154
	Per cent	1.9 %	5.9 %	3.0 %	1.7 %
Unclassified	No	150	113	83	170
	Per cent	1.7 %	1.3 %	0.9 %	1.9 %
<i>Artificially Fed</i>					
Respiratory	No	240	140	93	180
	Per cent	14.1 %	8.6 %	5.5 %	10.9 %
Gastrointestinal	No	33	129	74	35
	Per cent	2.2 %	7.5 %	4.3 %	2.2 %
Unclassified	No	28	34	39	38
	Per cent	1.6 %	2.0 %	2.2 %	2.1 %

July, and August, as summer, September, October, and November, as autumn, and December, January, and February, as winter. The

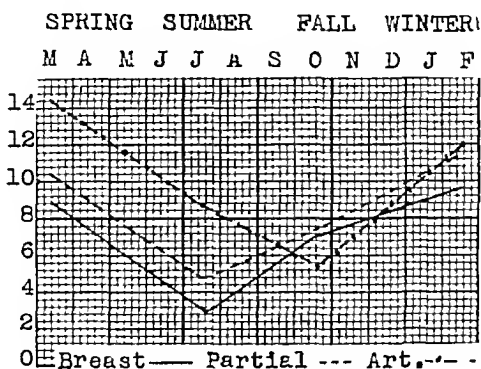


Chart 1—Seasonal morbidity from respiratory infections

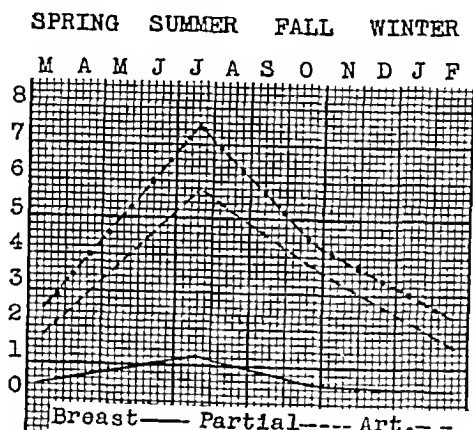


Chart 2—Seasonal morbidity from gastrointestinal infections

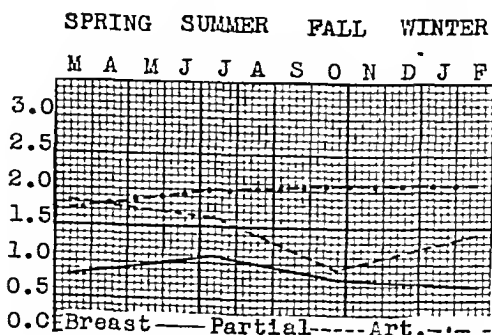


Chart 3—Seasonal morbidity from unclassified infections

exact number of cases is recorded for each season. Below this is given the percentage of these cases to the total number of infants in that group.

These percentages are also expressed graphically. In the charts however, the statistics are recorded on a monthly rather than a seasonal basis.

As reported in the previous paper there were 218 deaths during the five-year period, giving a total mortality of 1.1 per cent, or eleven deaths per thousand.

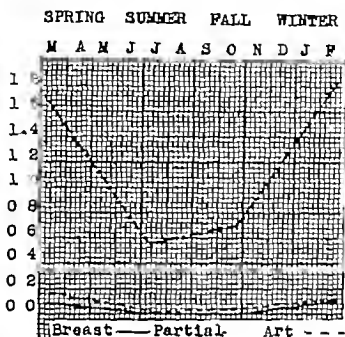


Chart 4.—Seasonal mortality from respiratory infections.

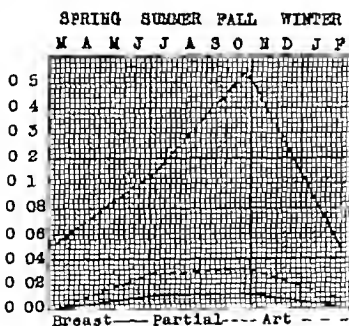


Chart 5.—Seasonal mortality from gastrointestinal infections.

Table II and Charts 4, 5, and 6 give the exact number of deaths by seasons with a percentage of total deaths (218) as in the morbidity. These percentages are also expressed graphically (by months).

DISCUSSION

The greatly increased morbidity and mortality of the artificially fed infant over the breast fed and partially breast fed child have been

discussed elsewhere and will not be repeated here. In all groups the respiratory infections are greatest in the spring, smallest during the summer, and increased during the fall and winter almost to the spring peak.

In gastrointestinal disturbances the curve for seasonal morbidity for the breast-fed baby is so low as to make it hard to record. There is a slightly higher incidence in the summer. Both the artificially and partially breast-fed groups show a low incidence in the spring, rising to an extreme peak in the summer and dropping through the fall and winter. Note that the total incidence of morbidity is twice as great in the respiratory disturbances as in the gastrointestinal.

In the unclassified infections the morbidity in the breast-fed group is low in the spring, fall, and winter, with a slight increase in the

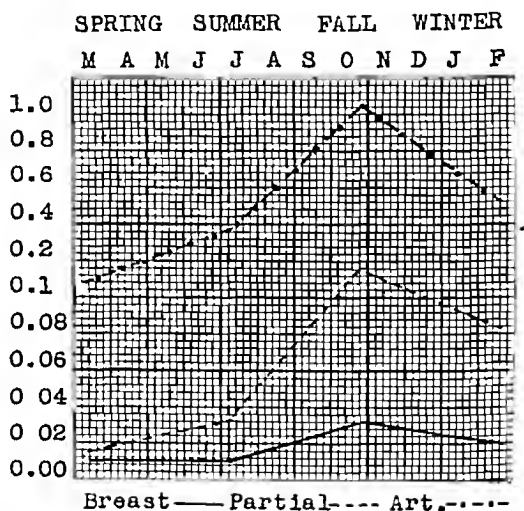


Chart 6—Seasonal mortality from unclassified infections.

summer. The partially breast-fed group shows an increase in the spring and winter, while the morbidity of the artificially fed group is low in the spring and higher in the summer, fall, and winter.

We may say, therefore, in general, that in all types of feeding the morbidity for respiratory infections is greatest in the spring, lowest in the summer, and increases through the fall and winter to the spring peak. The gastrointestinal disturbances are low in the winter and spring and reach an extreme peak in the summer, decreasing through the fall. The unclassified infections are lowest in the spring.

In the seasonal mortality the curves follow in general those for morbidity, except for gastrointestinal disturbances. For these the greatest mortality is in the early fall, or October, when the morbidity curve is falling. Note the greatly increased mortality of the artificially fed baby in all seasons. Also note that the respiratory infection mor-

tality is about three times that of the gastrointestinal infections. The mortality curve in the unclassified infections rises more abruptly in the winter than does the morbidity curve.

TABLE II
SEASONAL MORTALITY

		SPRING MAR. APR. MAY	SUMMER JUNE, JULY AUG.	FALL SEPT. OCT. NOV.	WINTER DEC. JAN. FEB.
<i>Breast Fed</i>					
Respiratory	No	1			3
	Per cent	0.01 %			0.03 %
Gastrointestinal	No		1	1	
	Per cent		0.01 %	0.01 %	
Unclassified	No	1	1	3	2
	Per cent	0.01 %	0.01 %	0.03 %	0.0 %
<i>Partially Breast Fed</i>					
Respiratory	No	15	6	7	17
	Per cent	0.10 %	0.061 %	0.085 %	0.021 %
Gastrointestinal	No		2	3	1
	Per cent		0.025 %	0.037 %	0.014 %
Unclassified	No	1	3	14	7
	Per cent	0.014 %	0.037 %	0.175 %	0.034 %
<i>Artificially Fed</i>					
Respiratory	No	30	10	11	31
	Per cent	1.76 %	0.59 %	0.64 %	1.82 %
Gastrointestinal	No	1	3	9	1
	Per cent	0.05 %	0.175 %	0.533 %	0.05 %
Unclassified	No	2	7	13	8
	Per cent	0.10 %	0.29 %	1.05 %	0.47 %

CONCLUSION

The seasonal incidence of morbidity and mortality in this group of infants does not differ materially from the generally accepted ideas. In general the seasonal curve is not affected in its contour by the type of feeding. The height of the curve, however, is continually lowest in all seasons in the breast fed infant.

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Pediatric Clinics

THE CHILDREN'S HOSPITAL [KING EDWARD VII MEMORIAL]

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History—The latter half of the eighteenth century was a momentous period in the foreign and domestic politics of Great Britain. Abroad, the American War of Independence was precipitated by a foolish King and his advisors, whilst at home there occurred the so called Industrial Revolution. The Birmingham Children's Hospital has an interesting connection with this revolution, a period which proved in the most literal sense of the word a golden age for all but the labouring classes. The acquisition of wealth was, however, not the sole pursuit of that age, there was also a veritable renaissance of learning which led to the foundation of many philosophical clubs of which the Lunar Society of Birmingham was one of the most famous. The members of this Society were, not unnaturally, labelled "lunatics," but its name was due to the fact that the meetings took place when the moon was at the full in order that the members, having dined at two o'clock in the afternoon, could reach home by the light of the moon and thus obtain protection from attacks by the footpads who, at that time, infested the town. The Society included amongst its members James Watt, the inventor of the steam engine, his partner, Matthew Boulton, who became famous as a maker of Sheffield plate, James Wedgwood, the founder of the great pottery firm of that name, Erasmus Darwin, grandfather of Charles Darwin, Joseph Priestley, the discoverer of oxygen, Francis Galton, the physicist, and William Withering, the greatest physician Birmingham has ever had. Withering not only introduced digitalis into medical practice, but he was also a great botanist and chemist, indeed, he it was who suggested to Priestley the line of research which led to the preparation of oxygen. So famous was Withering that when he lay a dying, a London contemporary who visited him is accredited with the aphorism, "The flower of English medicine is indeed withering." A meeting of the Lunar Society I am sure produced not only a good dinner, but also a feast of intellect and a flow of wit almost beyond imagination. It is because of this amazing collection of members that I like to think we can claim some slight association with the Lunar Society in the fact that the Hospital was opened on January 1, 1862, in the house which had been the home of Francis Galton—a house which incidentally has only disappeared within recent years to make way for a cinema!

This little institution of ten beds, founded largely as the result of the efforts of Dr T P Heslop, had as its expressed objects

- 1 To treat the sick children of the poor
- 2 To increase knowledge of disease and to provide for more efficient instruction of students.

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3 To diffuse among all classes knowledge of the management of infants and children during illness and to train women as children's nurses.

4 To treat diseases peculiar to children and not to deal with surgical conditions.

Except for a slight modification of the last these objects have been always kept in view although the instruction of students has only been achieved within recent years. The work of this small hospital increased so much that in 1870 a larger building was taken, which provided accommodation for sixty two beds, nearly one half of these now being devoted to the surgical conditions of childhood. In this building the work was carried on with varying fortunes for nearly half a century although long before the end of that time it was obvious that the building was totally unsuited for the work and it became quite clear that if paediatrics was ever to have any standing in Birmingham, a hospital worthy of the subject must be erected. Fortunately the members of the managing committee were men and women of vision and faith. They conceived a plan of a hospital of 150 beds which however for a few years it seemed impossible to implement but on the death of King Edward the Seventh in 1910 an appeal was made that a Children's Hospital should be built as a memorial to him. This appeal was successful building operations being started in 1911 only to be delayed by the European War and although patients were received in the new hospital in 1917 it was not until 1919 that it was formally opened by His Majesty the King and then only for 100 patients. Since that time the development of the hospital has been continuous the number of beds was increased to 160 in 1927 in 1924 an out patient department was opened in 1929 the number of beds was increased to 218 and an isolation block built in 1932 a new nurses home was built and plans are now prepared for a separate infants block which it is hoped may be ready for occupation in 1938 and which will bring up the number of beds to over 300. It is not anticipated that the hospital on its present site will ever increase much beyond that number of beds.

Hospital Practice in the United Kingdom.—Before describing the hospital it may be interesting to indicate some differences which hospital practice in the United Kingdom and in many but not all parts of the British Empire presents from that in America and elsewhere. First, our children's hospitals have been planned on general hospitals and therefore when fully equipped contain most of the departments usually associated with a general hospital and also certain departments which are not found in a general hospital. Thus in the Birmingham Children's Hospital there are

- 111 beds allotted to general medicine
- 61 beds allotted to general surgery
- 26 beds allotted to ear and throat
- 5 beds allotted to ophthalmology
- 3 beds allotted to dermatology
- 8 beds allotted to orthopaedics
- 20 beds allotted to private patients
- 14 beds allotted to infectious diseases

In addition there are large dental and orthoptic departments speech clinics for stammerers and children with palatal defects venereal disease clinic radiological light massage and remedial exercise departments bacteriological pathological, biochemical and pharmaceutical laboratories

Second, the members of the visiting medical staff with one exception are unsalaried although during the first six years of their service they receive a small honorarium of £40 (£200) per year. The only full time salaried visiting medical officer is the pathologist. Appointments to the visiting staff are made by the Board

of Management at an open election, certain fundamental qualifications being necessary before a candidate is eligible to compete for election. In the case of a physician this is Membership or Fellowship of one of the Royal Colleges of Physicians, and for a surgeon, Fellowship of one of the Royal Colleges of Surgeons. On first election the successful candidate works in the out patient department, but when he reaches a certain degree of seniority and as those senior to him retire, either voluntarily or under an age limit, he obtains charge of beds. In our hospital everyone is given charge of four beds on election and this number gradually increases, but in other hospitals there is a sharp dividing line between the senior members of the staff, who have charge of beds, and the junior members, who have charge of out patients. It thus follows that the available beds are split up between a large number of people and no one has a predominating number, for instance, we have four medical wards each containing from twenty five to thirty beds divided amongst six physicians. Each of the three senior physicians has one ward and the fourth ward is split up between the three junior physicians. The Professor of Children's Diseases has the right to have beds in the hospital but almost certainly the holder of this office will always be chosen from one of the physicians already attached to the hospital. There is no whole time Professor of Children's Diseases in Great Britain or Ireland and I know of only one children's hospital in which there is anything approaching the post of *chef de clinique* such as occurs in other parts of the world. The holder of the professorial chair is therefore dependent upon his colleagues for much of the material for teaching purposes, and such a state of affairs ought conceivably lead to difficulties, but I am happy to say that the attitude of my colleagues is one of helpfulness and cooperation and no such difficulties have ever arisen.

Third, all the members of the visiting medical staff make their living by consulting practice. The type of practice, so common in the United States and Canada, in which a paediatrician takes charge of the child throughout its childhood is unknown in this country, indeed, the visiting staffs of the majority of the teaching hospitals are debarred from general practice. For these reasons, and considering the large size of the staff of a children's hospital, many paediatricians do not limit their practice to children but are also attached to general hospitals and do consulting practice in adult medicine. There are many arguments both for and against the procedure although this is not the time to discuss them, but it may be pointed out as a curious and unfair anomaly that some general hospitals both in London and the provinces do not allow the physician in charge of the children's department to do adult practice, yet place no restriction on the general physicians who are allowed to, and do see, sick children.

Visiting and Resident Staff—The visiting medical staff consists of six physicians, six surgeons, two ear and throat surgeons, one orthopaedic surgeon, two ophthalmologists, three dental surgeons, one dermatologist, two radiologists, an anaesthetist, and a pathologist. There are also a group of part time salaried visiting officers who are not debarred from general practice—in fact some do not press a medical qualification—these include three anaesthetists, one ophthalmologist, a speech defect instructor, one orthodontist. In addition there are whole time salaried officers, none of whom has a medical qualification, amongst these are four biochemists, orthoptic instructors, masseuses. The resident staff is composed of a resident medical officer, a resident surgical officer, and a casualty surgeon, all of whom hold office from one to three years, an assistant resident medical officer who holds office for twelve months, two house physicians and three house surgeons who are elected every six months. The assistant medical officer and each of the house physicians and surgeons are attached definitely to one or more members of the visiting staff, and there is no rotation of service such as is often the case in America and Canada.

Undergraduate Teaching—Every medical student has to attend the hospital for instruction in his final and penultimate years, he has to attend twenty nine clinical lectures and demonstrations given by the professor and other members of the staff and in addition acts as clinical clerk in the wards for a period of two (shortly to be increased to three) months. The clinical clerks have to attend for the whole of every morning. There is no special examination in paediatrics, nor does it appear likely that one will materialise in the near future, and although a student may be asked questions in children's diseases in his examination, yet he may graduate without ever having his knowledge of paediatrics tested.

Hospital.—The hospital was planned with two objects in view: first to obtain the maximum amount of sunshine and for this purpose the main ward and the isolation block are built somewhat in the shape of a sector of a circle, the two arms of which face southeast and northwest respectively, second, to obtain the maximum amount of fresh air. A reference to the illustrations will show how the latter has been achieved. Each ward unit, of which there are eight consists of one large ward which contains twenty two beds arranged along one side only the opposite wall being almost entirely composed of folding windows which when opened and folded back make the ward a completely open air one. The small room (*d* in the photographs) in the middle of this wall was originally intended for a room in which dressings could be carried out actually it is now used for a warm room for children who require such an atmosphere. At the end of the main ward is a small room (*B* in the photographs) which was originally intended as an observation ward for doubtful infectious cases but is now used as a bedroom for nursing mothers or sick nurses. Near the entrance of the ward are grouped the ward kitchen linen room room for examination of urine and stools, and the infant ward. The latter (*C* in the photographs) contains eight cots, and this also is kept at a higher temperature than the main ward and although there are many windows all of which can be opened entirely, it is not possible to put the infants directly in the open air without taking them through the main ward.

In planning these wards we have made at least two errors. First the accommodation for infants is insufficient and also inadequate in that it does not allow for proper isolation. In building our new infants' ward block, we are planning to have two infants in a cubicle and one nurse to each cubicle. Second whilst it is possible to get children into the open air or even direct sunlight by wheeling their beds to the window side of the ward it is only possible to put them completely outside on the ground floor staggered balconies should have been provided for the other floors so that every child could be placed in the open air if necessary.

The isolation block *II* has the sisters' duty room in the middle on one side of this are a row of five rooms, divided from the sisters' room and from each other by walls chiefly made of glass, so that the sister can see the whole length of the ward from her desk on the other side the ward is not divided up. Running along the back of all these is a connecting corridor which in its turn connects with a sanitary annexe. Each of the little rooms contains running hot and cold water and a large window which opens so that the cot can be pushed outside. These rooms normally have one or two beds but will take three under pressure and are used to accommodate

(a) Children who develop infectious diseases in the hospital and are too ill to be transferred to the city infectious hospital.

(b) Children who on admission to hospital are known 'contacts' with infectious disease.

(c) Those with surgical conditions complicating infectious disease which cannot be adequately dealt with at the infectious hospital.

The large ward is used as a fallow ward to house contact children when an infection breaks out in a ward, or for the treatment of special epidemics with which the infectious hospital cannot deal adequately.

The wards on the one side and the nurses' home, *I*, on the other look out over a garden which in the spring and summer has all that charm and loveliness associated with an English garden and in which the children are allowed to play. Twenty years ago a large part of the garden was a slum promoting ill health in poor children, now its value as an educative and healing influence on the same type of children cannot possibly be overestimated.

One of the wards on the top floor is used as a private ward, and on this floor also the space which on the other floors is occupied by the infants' ward is used for surgical theatre accommodation. There are two theatres, one of which is specially equipped for ear, nose and throat surgery. The private ward differs little from the

G F E D

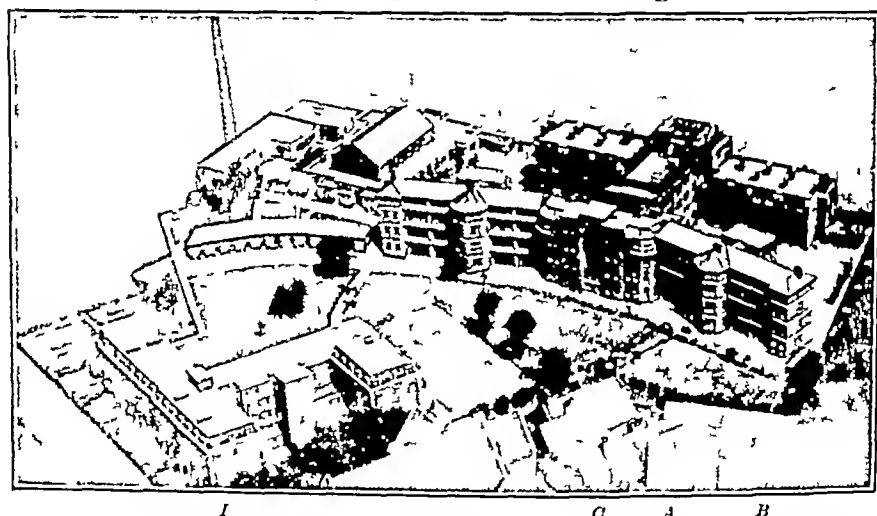


Fig 1—Aerial view of the hospital building. *A*, warm room. *B*, bedroom for nursing mothers or sick nurses. *C*, infant ward. *D*, administration block. *E*, out-patient department. *F*, pathological block. *G*, laundry and boiler house. *H*, isolation block. *I*, nurses' home.

other wards except that the main ward is broken up into three smaller units by glass partitions. Scarcely any provision has been made for the child's mother or nurse to remain with him, indeed, unless the mother is nursing the baby, this practice is discouraged, but it is probable that in the future this accommodation may become necessary. The hospital charge for a private patient is £1 14s 6d (\$23.50) a week, medical fees being charged in addition. Sometimes patients who cannot afford these charges are admitted to this ward, under such conditions the hospital fee is reduced to £3 3s 0d (\$16.00) per week, and medical fees are also reduced. This figure leaves the hospital a small margin of profit since the cost per bed in the whole hospital works out at £2 17s 6d (\$14.50) per week, incidentally, during 1934, 3,500 patients were treated in the hospital, the average length of their stay being twenty-one days.

The kitchens, dining rooms for nursing and resident staffs, quarters for resident medical officers, bedrooms for some nurses and for maids, together with the ad-

administrative offices, are in a block, *D* which roughly runs parallel with the ward block. There is a central milk room in the ward block where all the feedings for infants are prepared. The hospital obtains tuberculin tested milk from one herd of cows, but for greater security this is also pasteurized in the milk room. Every nurse during her training spends six weeks in this department so that she becomes familiar with the methods of milk preparation.

Connected with the main hospital block by a covered passage is a large out patient hall, *E* larger than is common in America. This department consists of a large central hall, grouped around which are consulting and examination rooms, almoners and registration offices, operating theatre isolation, plaster, and eye and ear and throat rooms. Adjoining the operating theatre is a ward of twelve beds in which children are housed for at least one night after operation for tonsils and adenoids. In the basement of this department is the pharmacy with its separate waiting hall a buffet where parents and children can obtain refreshment at a small cost biochemical

O 1 B

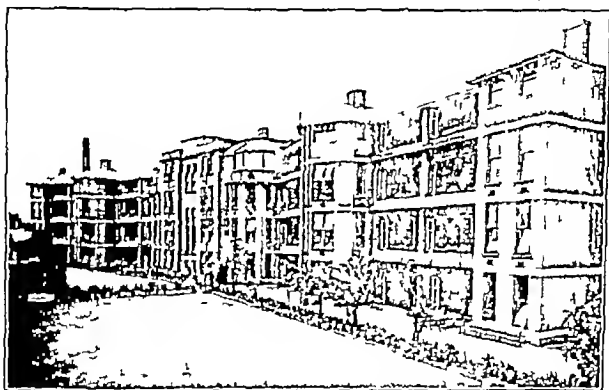


Fig. —View of ward block showing folding windows *A*, warm room *B* bedroom for nursing mothers or sick nurses *C* infant ward.

laboratories, workshops and storerooms. The size and work of the out patient department may be gathered from the fact that the number of patients attendances is over 100,000 a year and that in the same time 3,500 children pass through the small ward mentioned above.

The orthoptic department has a staff of four trainers and is a teaching school for orthoptic trainees. It deals with more than 150 children a year and is not only the largest but also was the first department of its kind in any children's hospital in the British Isles. Together with the orthodontic department it is at present located in some old dwelling houses in the hospital grounds which will later be replaced by new buildings.

The pathological laboratories, *F* are housed in a separate building and the increase of research work and workers in recent years has rendered these and the biochemical laboratories inadequate for their purpose. Close to this block is the laundry *G* in which all the hospital washing is done and in which something like three-quarters of a million pieces are washed annually.

Nursing Staff—The new nurses' home has accommodation for 120 nurses, all having single bedrooms, and in addition to recreation rooms there are classrooms, cookery school, and a lecture theatre equipped with epidiascopes and cinematograph which is used for lectures to nurses and medical students. Nurses accepted for training must be over the age of eighteen years and must produce satisfactory evidence of general education. The number of nurses in training is ninety-nine, the course lasts three years, at the end of which those who adopt nursing as a profession usually proceed to an adult hospital for further three or four years' training. There are thirty-three graduate nurses distributed as follows:

Administrative Sisters	5
Ward and Department Sisters	14
Staff Nurses	14

None is allowed to hold the post of "sister" unless she is a registered "adult" nurse and has had experience in nursing children. The majority of "staff nurses," i.e., the post immediately below that of sister, are registered "adult" nurses, some of whom have had previous experience in children's nursing, whilst occasionally one of our own graduate nurses occupies the post.

Any description of the hospital would be incomplete without mentioning two affiliated institutions. First, about three miles away, set in a park of 20 acres, is a continuation hospital containing ninety beds to which children with tuberculous bones and joints and rheumatic heart disease may be sent for a prolonged period. The system of treatment for acute rheumatism includes a stay of three months or longer in the children's hospital, then for suitable cases a period of six months to two years at this continuation hospital and then a residential school. Second, the president of the hospital, Mr C. Kunzle, a Birmingham citizen of Swiss nationality, owns a chateau at Davos, Switzerland, and during the last three years has received there over 100 children suffering from asthma, pulmonary fibrosis, emphysema, chronic cough, tuberculous peritonitis, tuberculous glands, etc., who have remained for varying periods of three months to two years. The children are under the care of Dr Burkhardt of the Pro Juventute Kinder Sanatorium, and the hospital supplies one sister, one graduate nurse, one teacher and two nurses in training.

Research—The hospital strives to live up to the object laid down by its founders "to increase the knowledge of disease in childhood" by stimulating research. The managing committee of the hospital spends on research what, for British hospitals, is a large sum of money, and in addition grants are made from the Medical Research Council and from the University Research Funds. A research scholarship of £100 (\$2,000) per annum is awarded on my recommendation, the present holder (Dr Carey Smallwood) is carrying out haematological research, facilities are also given for two other research workers to live and board in the hospital but without remuneration and at the moment there is a vacancy for a rheumatism research scholar for a period of two years at a salary of £300 (\$1,750) per annum. The senior biochemist (Dr E. M. Hickmans) receives a personal grant from the Medical Research Council on the understanding that she spends half her time in research. In the past a considerable amount of research work has been done on bone dyscrasias in general and on renal and ocular rickets in particular, in the course of which much valuable help has been received from the radiological department (Dr C. G. Teall and Dr E. Thorpe), coeliac disease and infantile atrophy. Amongst the subjects which have occupied our attention now and in recent years are the anaemias of infancy and childhood, the anti-anaemic factors of yeast, the lipids in anaemia, the problems of tuberculosis of the childhood type, the spread of ward infections

amongst infants the relation of vitamin A to coeliac disease the control of scurvy by ascorbic acid and the value of qualitative tests of ascorbic acid in the urine as an index of latent scurvy a comparison of the anti-rachitic effect of sunshine and skylight in Birmingham with that in the open country acute rheumatism

The hospital is delighted to receive accredited workers from overseas, either as research workers or graduate students, and it may be a matter of interest to note that our pathologist, who came from the Babies Hospital, New York, on the recommendation of Dr Rustin McIntosh and Dr Alan Brown, and the resident medical officer who was sent to us from Rochester N Y, by Dr S W Clausen, are Canadians and University of Toronto graduates.

I have now been on the staff of the Children's Hospital for twenty four years and for a great part of that time have had a share in the development of its policy therefore any attempt on my part to assess the hospital's progress and contributions to paediatrics, and to apportion praise for this, is a matter of considerable difficulty which I approach with diffidence. There is no doubt that in the pursuit of science, buildings and equipment are always secondary considerations and that it is men and women who count yet in spite of that truism, buildings and equipment do play an important part. At any rate prior to its move into its present quarters the Birmingham Children's Hospital was a parochial institution scarcely known outside Birmingham and regarded by the general hospitals of the city as a poor show which "cut no ice," and its staff had made but few contributions to paediatric research. After the War, however a new era opened and the hospital began to take its proper place in the city, the reasons for this being

(1) The vision of the managing committee and medical staff of a decade previously in planning and providing the nucleus of the present buildings.

(2) The appointment as superintendent of a young man of energy and vision who had been thoroughly trained in hospital management (Mr H F Shrimpton) and who fortunately still remains with us to guide our policy.

(3) The realization by certain members of the medical staff that in spite of the years that the locusts had eaten on active service there were some problems worth attempting to solve in the difficult times of peace.

Some two or three years later two other appointments were made which greatly stimulated our work, namely that of our present nursing superintendent (Miss E. M. Cockeram) and a biochemist (Dr E M Hickmans). In these early post war years also there sprang up a healthy friendly jealousy of Glasgow Children's Hospital, and during this time we believed that by our clinical work and investigations we were beginning to earn a reputation for the hospital. It was therefore a great blow to find that the hospital was not even mentioned in the list of British Children's Hospitals which appeared in Abt's *Paediatrics*. Chronologically the next most important factor in stimulating the development of the scientific side of the hospital was a visit I paid to the United States and Canada in 1925 in the course of which many valuable lessons were obtained and great inspiration received. On my way home I read with great interest Abraham Flexner's *Medical Education* but his statement concerning Great Britain that 'paediatrics with the exception already noted (Glasgow) does not in the modern sense exist' fanned the smouldering fire of jealousy of Glasgow into a flame of intense envy and anger. Although this statement seemed to me a trifle unfair I registered a vow that I would try my best to stimulate my colleagues to wipe away the reproach. It is not for me to say whether we have succeeded but the fact that the Editor has asked for this article and that we are delighted to receive many visitors from overseas makes me feel that we are beginning to breathe the same rarefied atmosphere in which our friends in Glasgow so deservedly

live! The last point which I would mention in the development of our clinic is the fact that in 1928 "in view of the importance of the research work carried on at the (Children's Hospital)" the University of Birmingham raised the status of the lecturer in diseases of childhood to that of professor, bringing the number of chairs in this subject in the British Isles to four (five since 1933)

Conclusion—The Editor has asked me to describe something of the spirit of our hospital. To put into words and define the things of the spirit is always a difficult, nay, sometimes an impossible task, but to anyone who asks "can any good thing come out of Birmingham?" I would reply "come and see," for we should be delighted to demonstrate the spirit of the hospital. This spirit may, I believe, be expressed in four words—happiness, loyalty, enquiry, service—all of which are essentials if any children's hospital is adequately to fulfil its purpose. This hospital is a very happy place, we try by our actions to instil into the children that the hospital is a place in which to get and to keep well and that health and happiness go together. To this end the discipline is not rigid, all treatment and investigations being made as much a game as possible, and for this reason we do not hesitate to accept children for treatment in our speech defect and squint clinics who are otherwise in perfect health. The idea that attendance at a hospital makes a child fainful and neurotic has been, in our view, completely exploded. Loyalty the spirit of loyalty and helpfulness extends throughout all departments of the hospital, administrative, nursing, medical, engineering, etc., everyone strives to make this hospital if possible the best hospital for children in this country. Enquiry research is encouraged in every way, both in the wards and in the laboratories because we realize that without this stimulus the treatment of disease becomes stereotyped and eventually sterile, moreover, research is not limited to medical problems, and I might perhaps mention that recently it has included the best type of paint for wall surfaces and methods of cleansing and sterilizing babies' napkins. Finally, as with all who work for the sick, we have but one real object and that is to render the best service in our power to sick children and to give them the greatest chance to recover their health in the happiest possible surroundings.

Critical Review

PROGRESS OF PUBLIC HEALTH AS IT RELATES TO THE CHILD

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MORTALITY AND MORBIDITY

THE picture presented by mortality statistics in the United States for 1934 is somewhat less satisfactory than for 1933 or 1932 but rates were in general below those for 1931 and previous years. Preliminary figures made available by the United States Public Health Service¹ show a combined infant mortality rate of 58 for 1934 as compared with 56 for 1933, 57 for 1932, 61 for 1931, and 62 for 1930. Rates for diarrhea and enteritis in children under two years of age were slightly higher than in the preceding two years but still much lower than in 1931 or 1930. Deaths from pneumonia were increased over the two preceding years but the rates for influenza and tuberculosis showed a marked decline. The rates for diphtheria, scarlet fever, typhoid fever and poliomyelitis were all favorable. The two most striking increases were in the rates for measles and whooping cough, both of which rates were much higher than in any recent year. The actual rates for these diseases in the twenty-five states having 1934 figures available are shown in Table I for each of the past five years. These are population rates—age distributions are not yet available.

TABLE I

MORTALITY FROM CERTAIN CAUSES IN THE 25 STATES OF THE UNITED STATES WITH AVAILABLE DATA BY YEAR 1930-1934

(Population July 1, 1934—80,813,000 Live Births 1934—1,400,000)

DEATHS	1934	1933	1932	1931	1930
<i>Per 1,000 Live Births</i>					
Total infant mortality	58.0	56.0	57.0	61.0	62.0
Maternal mortality	5.4	5.0	5.0	6.2	6.2
<i>Per 100,000 Population</i>					
Diarrhea and enteritis (under 2 yr.)	11.1	10.0	10.3	14.0	17.8
Measles	4.1	1.0	1.5	2.5	2.9
Whooping cough	5.1	3.1	4.1	7.5	4.1
Scarlet fever	2.0	2.0	2.1	1.1	1.9
Diphtheria	2.7	2.9	3.8	4.1	4.0
Acute anterior poliomyelitis	0.0	0.0	0.1	1.9	1.1
Meningococcus meningitis	0.8	1.0	1.3	2.1	3.1
Influenza	15.1	17.7	27.3	24.8	18.5
Pneumonia, all forms	78.0	69.3	77.1	81.1	83.0
Tuberculosis, all forms	54.3	50.6	60.0	64.7	68.0

Figures taken from Public Health Reports, U. S. Public Health Service 50: No. 17, April 26, 1935. The states included are Alabama, California, Connecticut, District of Columbia, Georgia, Idaho, Indiana, Iowa, Kansas, Louisiana, Maryland, Michigan, Minnesota, Montana, Nebraska, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, South Dakota, Tennessee, Virginia, West Virginia and Wisconsin (Mississippi, Illinois, and North Carolina are also included in some of the rates.)

Diphtheria death rates for the country as a whole have not declined as rapidly in the past four years as results in those states actively pressing for preschool child immunization have shown to be possible. This fact explains the selection of diphtheria prevention by the Committee of State and Provincial Health Authorities of North America as the subject for special emphasis in May Day health activities this year. Another incentive to renewed efforts toward securing a population immunized against this disease comes from the simplification of procedure incident to the perfection of alum-precipitated toxoid. The adoption of this agent as the one of choice for public health purposes seems to be generally favored at the present time. Its safety and effectiveness, used in a single injection of 1 c.c. (7.5 to 100 units) have apparently been adequately demonstrated²⁻⁶.

As to the incidence of reportable illnesses, measles and whooping cough were unusually prevalent throughout the country, accounting for the high specific death rates already referred to and probably also to a degree for the higher pneumonia rate. Polymyelitis showed a high incidence in the Pacific and Mountain states, but the general picture throughout the country was not altered. Influenza remained generally inactive throughout the year, but 1935 opened with a mild wave of activity in progress. Scarlet fever also had not been prevalent but was generally on the increase at the beginning of 1935.

Exclusive of data on reportable diseases which, being communicable, tend to vary in incidence from year to year, and in contrast to the large mass of statistical data available on mortality rates, there have never been available any adequate data on the incidence of illness from different causes and among different age groups. Barring a few local studies such as those in Hagerstown, Md., very few investigations have been made of morbidity. Collins⁷ has recently published extensive figures collected by the United States Public Health Service on the number and type of illnesses occurring within a given year among 9,000 families visited every two to four months, resident in 130 localities in eighteen different states and comprising 39,185 individuals. A comparison of the incidence of illness discovered in this way may be made with the mortality rates for corresponding states to give a rough picture of the expected fatality from different conditions at different ages. For example at all ages collectively, respiratory diseases in this study represented the same proportion of all illnesses, as they represented of all deaths in the corresponding states, but they constituted a much higher proportion of illnesses than deaths at each age subdivision of childhood. It appears that illness rates are highest under five years and next between five and ten years of age, whereas death rates are higher after fifty-five years than under five and are extremely low between five and ten years. The fatality of illness is higher after fifty-five years than at any earlier age.* In the years before maturity, however, the general fatality of illness is highest under five years and lowest between five and ten years.

Such studies if conducted at regular intervals, would give valuable information as to the changing prevalence and severity of different diseases, and offer a rough measure of the progress made in the prevention or modification of each.

*In this comparison deaths under one year are averaged into the first five. These statements would not apply if the first year were considered separately.

EFFECT OF DEPRESSION ON THE HEALTH AND GROWTH OF CHILDREN

Eliot reviewed the literature on this subject in this series of critical reviews last year.⁸ Further evidence has been amassed during the year pointing to higher illness rates among the indigent than among the general population, and one such report⁹ indicates that these rates are higher in those families made poor by the depression than in those previously accustomed to a low standard of living. It has always been possible to demonstrate higher illness rates, higher mortality and poorer standards of growth among the low income classes than among the well-to-do, and as the proportion of the population in the lower income brackets increases, it is reasonable to assume that the health and growth of certain children are being adversely affected. A comparison of large groups including all classes today with similar groups during prosperous years, however, need not demonstrate these effects. The general trend toward better hygiene and nutrition operating with the majority of children may mask the adverse influences upon the children of the unemployed or poorly employed who are still in the minority. Actually many investigators have been unable to demonstrate any mass evidence of retardation of growth among large groups of children after five years of continuing severe economic stringency. For example, Palmer¹⁰ has made a comparison of annual weight gains of elementary school children in Hagerstown, Md. in two periods: the first, 1921-1927 and the second 1933-1934. He found that the increments, while on the average definitely smaller for each grade in the latter period, were not smaller than occurred in single prosperous years. Here also the gains were strikingly smaller for the children of persons receiving aid than for those not so situated, but this difference was no wider than between similar groups in prosperous years. Newman¹¹ also reports similar findings in Great Britain, namely, that the depression has not measurably increased the amount of illness or malnutrition or the number of deaths among children—quoting from his report: “the general health and nutrition of the population of England and Wales, taken as a whole, was well maintained in 1933.” There can be no question that the nutrition of the English people is better today than at any past period of which we have record.

This circumstance is due to the increased care and devotion of the mothers and teachers to manifold forms of voluntary service and to the public provision of insurance benefit, school feeding and medical supervision. We are therefore not warranted in being too complacent, but there is nevertheless justification for real satisfaction in the net results of community efforts to provide for the physical needs of children.

PUBLIC HEALTH SERVICES

In the first review in this series¹² it was pointed out that changes incident to the depression had not only interrupted progress in the development of state, municipal, and private services for the betterment of child health, but had actually caused serious interference with the activities of those already established in many parts of the country. In the second review⁸ the changes incident to the depression were dealt with in more detail, and it was made evident that the facilities for meeting the health and medical needs of children in large sections of the country were far from adequate. Appropriations and expen-

of Motherhood and Infancy, but in general, emphasis on preventive medicine has lagged. It is hoped that the new Institute of Hygiene and Public Health in Rome will stimulate interest in this work. Italy has recently greatly extended the protection afforded working mothers through a decree¹⁸ which provides for compulsory leave of absence from work before and after confinement, opportunity for nursing, insurance benefits, and investigation of maternal deaths.

Sweden's system of maternity benefits is an example of social insurance supplemented by national treasury contributions. Uninsured women with low incomes receive cash benefits for thirty days at the time of confinement, while insured industrial workers receive these for fifty-six days and in addition free midwife attendance, or hospital care if needed. Application must be made sixty days before the expected confinement, so that some prenatal care and plans for adequate delivery can be arranged. This system also allows for subsequent enrollment of the child in child health centers.

It is most difficult to appraise the value of health services from written reports. The plan may appear excellent on paper, but much depends upon the quality of work done, especially upon the training and ability of personnel, and one cannot make an estimate of these without close observation of work in progress. When political considerations dominate, the reporting evaluation is even more difficult. One even questions whether the reports of foreign visitors who acquire their information from hasty prearranged inspections or conversations with officials are really indicative of actual conditions. Reports from Soviet Russia relating to the progress of child health work bring all these questions vividly to mind. The observations of Newsholme, however, are of great interest.¹⁹

Child health activities in Soviet Russia have advanced from almost negligible levels to most extensive proportions under governmental auspices during recent years. This progress has been greatly facilitated by the virtual transfer of the care and control of children from parents to the state and the increased concentration of infants and children in public nurseries, schools and camps. It has gone hand in hand with welfare legislation affecting the economic and social status of women during pregnancy, the availability of medical care and the extent of health education. It has obviously been retarded by the dearth of adequately trained physicians and nurses. To show the rapidity of change there were in the towns of R S F S R * in 1932 263,000 beds in crèches as against 34,000 five years previously, and there were in villages in the same year 329,000 permanent and 3,500,000 seasonal beds as against 2,500 permanent and 101,000 seasonal beds five years earlier. Crèches house infants from two months to three years, sometimes to five years of age, while their mothers work in industry. Health service is provided in connection with these, as well as in connection with kindergartens, which care for children from the ages of three to seven years, and schools and camps, which care for older children. Free attendance at infant consultation centers is also generally provided and is often made a condition of the mother's receiving maternity benefits. Newsholme states that the training, hygiene, and precautions against infection in the crèches are intelligent and "the quality of the provisions made for the hygienic and

*Russian Socialist Federated Soviet Republics

medical care of infants bears comparison with any similar arrangements in western countries, and in quantity it is vastly greater."

There is in Russia no separation between clinical and preventive medicine because both institutional and domiciliary care have been socialized. There is reported to be close cooperation between home medical attendance, and the health work in crèches and consultation centers.

Care of maternity in Soviet Russia is of special interest because of the attention which this subject deserves and is receiving in the United States. About 90 per cent of births in cities in Russia are now in institutions, new maternity hospitals having been provided on a liberal scale. Special consultation centers for pregnant women have also been established in all large cities. In rural areas however, only about 20 per cent of deliveries are in institutions. Since the great majority of women in these areas are dependent upon midwives or relatives the government has recognized the urgent need for more adequately trained midwives by providing a number of training centers. Insurance provides women in industry with extensive maternity benefits including full wages during absence from work due to pregnancy and confinement and money allowances during the nursing period. Infant mortality was reported for European Russia as 275 deaths per 1000 live births in 1913, 186 in 1927 and 141 in 1930. The rate for Moscow was 130.9 and for Leningrad, 141.0 in 1929. The birth rate in these cities in the same year was 22 and 22.1 respectively, this despite the fact that in Moscow recorded abortions were 61 per cent in excess of normal births. Abortions were estimated to be ten times as numerous in 1929 as they were in 1922. Newsholme's description of medical education under the new regime and experience with regimentation of medical services elsewhere lead one to be somewhat skeptical as to the present quality of the various medical services described. One cannot doubt, however, that present conditions represent real progress.

There would seem to be little doubt that America has in recent years made more progress in the study of the child, especially of his health and medical needs, than has any other country. We undoubtedly have more physicians and other workers well equipped as specialists in the care of children. This review of activities in foreign countries raises the question as to whether we have as seriously faced the problem of making preventive health services, as well as medical services available to all classes in all communities. With far fewer resources and greater handicaps as to adequacy of trained personnel, it would seem that other countries have been attempting to do more to assure a minimum of health protection to all. These considerations give point to the plans of our federal government for promoting maternal and child health and for general public health protection as embodied in the present revision of the Social Security Bill.

THE SOCIAL SECURITY BILL

The House of Representatives has recently passed the so-called "Social Security Bill" (H. R. 7260) and at the present writing this bill is awaiting consideration by the Senate Finance Committee. This is an omnibus bill providing the means for protection against a variety of social hazards, a number of which have indirect bearing on child health but we are here concerned primarily with those provisions for

direct maternal and child health and public health services. Title V of this bill, "Grants to States for Maternal and Child Welfare," is divided into five parts. Part 1, "Maternal and Child Health Services," makes an annual appropriation of \$3,800,000 for payments to states to carry out suitable plans for such services. Twenty thousand dollars is granted directly to each State and \$1,800,000 apportioned on the basis of proportion of live births in each state. Only such portion of these allotments shall be paid to each state as does not exceed one-half of the total sum expended by the state exclusively for carrying out the accepted plans. An additional \$980,000 may be allotted by the Secretary of Labor without regard to the amount of state contributions on the basis of financial need. This equalization fund takes into account the greater need of health services where resources are least adequate. Receipt of these sums is made dependent upon suitable administration, supervision, reports, cooperation with medical, nursing, and welfare groups, etc. Part 2 of Title V, "Services for Crippled Children," appropriates a sum of \$2,850,000 annually to enable "each state to extend and improve (especially in rural areas and in areas suffering from severe economic distress) services for locating crippled children, and for providing medical, surgical, corrective, and other services and care, " This sum is to be allotted, \$20,000 to each state and the remainder according to need, but in this case the amount paid shall not exceed one-half of the total sum expended. Part 3, "Child Welfare Services," appropriates \$1,500,000 for cooperation with state public welfare agencies, \$10,000 to each state and the balance on the basis of rural population. Part 4 increases the present grants for vocational rehabilitation, and Part 5 provides \$425,000 "for all necessary expenses of the Children's Bureau in administering the provisions of this title." Oddly enough this provision for administration is made for one year only, whereas the title to be administered provides continuing services.

Title VI of the "Social Security Act," entitled "Public Health Work," appropriates \$8,000,000 for "assisting states, counties, health districts, and other political subdivisions of the states in establishing and maintaining adequate public health services, including the training of personnel." The primary purpose of this title is to secure for a fair larger proportion of the counties a full-time public health organization, qualified to provide the essential services. The amount allotted in this case is determined by population, special health problems, and financial needs, matching with local funds is not required. An additional \$2,000,000 is provided for expenditure by the Public Health Service for investigation of disease and problems of sanitation, etc.

Thus a total of about \$17,000,000 is appropriated annually for health services, \$7,000,000 under Title V for maternal and child health and care of crippled children to be administered by the Children's Bureau, and \$10,000,000 under Title VI to be administered by the United States Public Health Service for general public health enterprises. Consideration is given in the bill to the uneven development of these services in different parts of the country, and especially to their general inadequacy in rural communities. It is also recognized that those communities least able to finance improvements are, in general, those most in need of strengthening their facilities. No consistent principle is

followed, however, as to the amount of local participation in carrying the costs of necessary services required under the different sections of the bill. It is provided that the bulk of the funds shall be spent locally under the direction of the states with considerable latitude as to programs and services but that certain standards shall be required by the federal agency.

The House of Delegates of the American Medical Association in special session went on record⁴⁰ as opposed to the administration of any health service by a lay bureau and specifically deplored and protested those sections of the 'Social Security Act' (the original bill S 1130) "which place in the Children's Bureau of the Department of Labor the responsibility for the administration of funds for these purposes" (medical services for crippled children and for the preservation of child health and maternal health). However at the Senate Finance Committee hearings on this original bill a large number of physicians prominent in the field of pediatrics, recorded their approval of these health provisions. The organization of the federal government is such that the division of administrative responsibility between the two departments seems to be entirely logical and most certain to secure well planned and supervised service. The assistant director of the Children's Bureau and the acting director of the Division of Maternal and Child Health are pediatricians with outstanding records of accomplishment and with the confidence of the profession. Title V will most certainly be administered by this Bureau in close cooperation with and in many instances be applied through, the health units operated under Title VI by the Public Health Service.

Some may seriously question the desirability of the federal government's further participation in local services which the Social Security Act obviously provides, and many are concerned as to the economic implications of some of the other titles of this bill. The appropriations under Titles V and VI for health work are however relatively small. The health conditions in one section of the country are of vital concern to all others, and the problems in some sections are far more difficult than in others, a small equalization fund therefore seems warranted. Furthermore the federal government can make available expert advice and general information which local communities are often not in a position to secure for themselves. There is every indication that both federal departments administering the health provisions under discussion will grant the widest local autonomy consistent with the maintenance of a high quality of work and a suitably trained and qualified personnel.*

HOUSING

Relatively little attention has been given in the past by public health authorities in this country to the effect of bad housing conditions upon child health, except so far as they concern water supply, sewage and garbage disposal, or adequate cubic feet of air space. It has been noted that in England health authorities have been placing great emphasis upon slum clearance and low rent suburban residence building as a public health measure of importance. Other countries in Europe

The act as at present written unfortunately withholds from the Children's Bureau any administrative control over the selection, tenure of office, and compensation of personnel secured under these grants (Title V Sec. 503)

have been giving adequate housing considerable attention, and the accomplishments of Vienna are of special interest²¹. A new interest in this subject has recently been developing in this country, primarily as a result of the search for useful public works projects. Health officers have begun to realize the possibilities for improving public health through encouragement of slum clearance campaigns, and a number of studies on the relation of housing to health have appeared in public health journals.

It is not difficult to demonstrate a striking correlation between residence in slum areas²² and abnormally high morbidity and mortality rates, but it is rather difficult to demonstrate that these relationships are due to the housing conditions per se, and not to regularly associated conditions such as race, ignorance, poverty, and overcrowding. Health authorities have not felt certain that without changing these other conditions, mere transference of families from dilapidated slum buildings to modern tenements would materially improve health conditions. Recent studies²³ do suggest, however, that the condition of the house itself and its immediate surroundings are of real importance and that the transference of families from condemned buildings to modern low-cost structures results in an immediate and definite improvement in mortality and morbidity rates. There are of course accompanying changes in living conditions which are inevitable and which may explain the improvement, but these desirable changes are not easily secured without the housing program.

PARTICIPATION OF PRACTICING PHYSICIANS

During the late twenties there was evident in many communities a determination on the part of public health authorities to achieve certain goals, as for example, the immunization of the child population or the examination of the preschool children, by reliance upon publicly supported agencies. This policy was never prosecuted to the point of serving adequately the child population or of closing a fruitful field to the private practitioner, as the White House Conference survey²⁴ clearly demonstrated. It was nevertheless carried beyond the stage of demonstration and offered to many who might better have turned to their personal physicians. The economic difficulties of the early thirties have operated to correct this trend. The restriction of public health funds has in many instances forced the health officer to relinquish routine services and to look upon himself as a champion and promoter of these services rather than their provider. On the other hand, economic conditions and the low incidence of illness have made preventive health procedures seem more worthy of cultivation to practicing physicians. The same forces have, however, increased the proportion of those unable to pay for preventive procedures. As a result, there have been many evidences of cooperation between departments of health and local medical societies in work directed toward the establishment of more satisfactory relations, and especially toward a greater participation by private practitioners in broad health movements.

An article by the Bureau of Medical Economics of the American Medical Association²⁵ discusses a number of local movements and indicates their wide divergence in method but their common purpose.

Space does not permit a consideration of the effects upon child health services of the various plans now in operation, or the direction

of trends in different communities. So far as they strengthen the ties between the personal physician and the family and increase rather than diminish the acceptance of the important health procedures these changes may be accounted evidences of progress.

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American Academy of Pediatrics

Proceedings

FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

JUNE 11 AND 12, 1934

Panel Discussion on the Ductless Glands

Leader R G Hoskins, M D, Boston, Mass Assistants C A Aldrich, M D, Winnetka, Ill, J B Collip, M D, Montreal, Que, Murray B Gordon, M D, Brooklyn, N Y, Henry F Helmholtz, M D, Rochester, Minn, Irvine McQuarrie, M D, Minneapolis, Minn, A Graeme Mitchell, M D, Cincinnati, Ohio, E Kost Shelton, M D, Santa Barbara, Calif, and Fritz B Talbot, M D, Boston, Mass

The Panel Discussion on Ductless Glands was called to order at 11 30 AM by R G Hoskins, M D, Harvard Medical School

CHAIRMAN HOSKINS—There is something new abroad in the land known as "progressive education." I know little about the progressive educators, but they have introduced into American educational circles the so called "panel discussion." The idea of the panel discussion is to get together a group of people, preferably people who have had some experience and ideas on some problem worth discussing and have them "thresh out" the subject in public

As the idea comes into medical meetings, it seems to encounter a serious difficulty everyone wants to make a set speech, that is contrary to the spirit of the panel discussion We shall aim to interrupt by impertinent questions any man who starts going too strongly on such a bent It is part of the technique of the panel discussion to have questions come in written form from the audience If time and ability of the group serve, we shall undertake to answer any questions that are thus presented

(The members of the group were introduced)

Dr Shelton claims to have no competence as a pediatrician and comes before you strictly as an endocrinologist Apropos to his claim of knowing nothing about pediatrics—he practiced medicine in a Colorado community for seventeen years—delivered babies, treated epidemics, served as guide, counsellor and friend to the community for a hundred miles around I don't know whether they had pediatrics in that community but, if they did, Dr Shelton was the man who supplied the pediatrics

The next man in the group is Dr Irvine McQuarrie, professor of pediatrics at Minneapolis It would be impertinent on my part to introduce him to this audience

Professor Collip is professor of biochemistry at McGill He is the first man, so far as I know, to have successfully organized research in physiology on a whole-sale plan His work on insulin and on "parathormone" is known to all of you

The interlocutor on the program has, for a number of years and in a fairly in offensive way practiced physiology. In the meanwhile, for the past half dozen years, he has been practicing what I suppose could best be characterized as research psychiatry (Dr Helmholtz, Dr Mitchell, and Dr Gordon were then introduced.)

I have asked Dr Helmholtz to open the discussion by presenting the general subject of endocrinology as it appears to a podiatrist who says he does not know much about endocrinology. He is going to survey for you the field as it looks to the pediatrician. We are in a very peculiar position in this country economically and scientifically. Economically we are surrounded with great abundance—shoe factories that can make twice as many shoes as we can use. 50 per cent more farms than we can use. Half the farmers in this country practicing agriculture as they do could feed everybody in the country. We have an abundance in the mass and scarcity among individuals. Our problem of distribution is a trying one sadly in need of a much better solution. We are in a good deal the same situation in physiology, and particularly in endocrinology. We have in endocrinology at the present time, a vast amount of perfectly substantial, well authenticated material, most of which has not yet got into circulation among the men who can make practical use of it. A good deal of this is still in the form of raw material which will have to be "processed" before it can be put to actual clinical use.

DR HELMHOLTZ—The topic assigned to me is relatively simple because it is limited to a discussion of those disturbances which have been proved to be due to hyperfunction or hypofunction of a gland of internal secretion and for which the appropriate hormone is available for general use or for which surgical interference is possible. I shall discuss only those endocrine disturbances controlled in investigative studies of which have been carried on over a sufficiently long experimental period to make possible a routine of treatment that can be carried out by the pediatrician.

A great many endocrine products have been placed on the market without adequate control and have been recommended for numerous types of dysfunction. Some of these products, in which the active principle has been isolated only in the last few years, are not yet ready for use by the practical pediatrician. It is about this latter group that most of our attention will center this morning.

It is my present opinion that there are just three hormones concerning which investigation has been sufficiently controlled that they can be unreservedly recommended for use in pediatric practice. I refer to the hormone of the thyroid gland, thyroxin, that of the pancreas, insulin, and that of the posterior lobe of the pituitary gland, pitressin.

The thyroid hormone was isolated in crystalline form by Kendall. Thyroxin must be given intravenously and, on this account, has not displaced the desiccated gland in the treatment of thyroid hypofunction. Clinical manifestations of thyroid deficiency depend on the age at which the condition develops. If the condition is congenital, the typical picture of cretinism soon becomes evident. Reserves of thyroid secretion from the mother delay the manifestation of insufficiency until the child is from three to four months old. The picture of deficiency is so characteristic that it should not be mistaken for anything else. If the patient has normal thyroid secretion for a few months, and then as a result of infection or some other factor the thyroid gland ceases to make thyroxin, infantile myxedema develops. If destruction of thyroid tissue comes after years of normal secretion, the juvenile type of hypothyroidism develops. The earlier insufficiency develops and persists during the first two years of life the less likelihood is there of normal mental development in spite of normal physical growth. Early diagnosis and administration of thyroid hormone is most important.

In a series of about 157 cases of exophthalmic goiter encountered at the clinic, the metabolic rate before operation averaged +47 per cent before the use of iodine, since iodine has been given, the average metabolic rate before operation has been reduced to +16 per cent. The mortality rate, which was about 5 per cent before the institution of treatment by iodine, has been reduced to less than 2.5 per cent. Of those patients who were not operated on, two who refused operation died within a year. Geographic situation apparently plays a large part in the severity of this disease, which fact becomes evident when one compares the figures from the region of the Great Lakes with those of the Atlantic seaboard.

The use of insulin in diabetes is so standardized that at present it can be used by anyone who can carry out routine examinations for sugar and who can prescribe a weighed diet. Some have gone so far as to prescribe a regular diet and to control glucosuria by sufficient administration of insulin. The clinical entity, hyperinsulinism, which condition is the result of tumor of the islands of Langerhans, is now generally recognized. Not so common as hyperthyroidism, it nevertheless is a definite condition, which can be cured by surgical removal of the pancreatic tumor. The relation of the hypoglycemia to convulsive disorders is of special interest to the pediatrician.

A third gland which gives well recognized symptoms of both hypofunction and hyperfunction is the parathyroid. What relationship there is between hypofunction of the parathyroid gland and infantile tetany at present has not been determined. That the parathyroid gland may play an intermediary part seems probable. Marked hypertrophy of this gland in experimental rickets of chickens is evidence of the effect. Infantile tetany, as well as idiopathic tetany of older children, is at present not permanently controlled by parathyroid extract, and they seem to recur after a period of return to normal. Hypersecretion of the parathyroid gland has been shown to produce a great variety of clinical symptoms, most outstanding of which are hypercalcemia, and hypophosphatemia and hypersecretion in the urine of both calcium and phosphorus. The disease of bone, osteitis fibrosa cystica, and simple osteoporosis without cysts, and renal lesions of different types are all the result of hyperfunction of the gland, usually caused by an adenoma. Successful removal of the tumor will cure the disease unless the kidneys have been too badly injured.

Crystalline cortin is also available at present, but Addison's disease is practically unknown in childhood, so that it does not concern us at present. Whether the syndrome of precocious sexual development, hirsutism, adiposity, and hypertension is due to excessive secretion of the gland is at present unknown, it is known, however, that removal of the suprarenal tumor will relieve the condition and bring about return to normal.

With regard to the use of pitressin nothing need be said. It is well known that diabetes insipidus can be controlled temporarily by the use of hypodermic injections of this substance.

The pituitary gland recently has been studied intensively, and new products have been produced which affect the pancreas and the thyroid, pituitary, mammary, and sexual glands. At present it seems advisable, from the point of view of the practical pediatrician, to await the results of carefully controlled studies before using such products.

With regard to the practical application of both insulin and pitressin, it is to be hoped that a better way of administering them will be found than by the hypodermic route, so that children will not be in constant fear of the hypodermic needle.

DR McQUARRIE—How would epinephrine be classified, as a drug or hormone?

DR HELMHOLZ—We use it as a drug rather than as a hormone. It has been used in Addison's disease very extensively with practically no results.

CHAIRMAN HOSKINS—Dr Shelton, what is your impression of the implication that hypothyroidism is a single entity?

DR SHELTON—Hypothyroidism can give rise to different clinical pictures. In the first place during the stage of development, one should think of the thyroid hormone as one of tissue differentiation. If the inherent destiny of the germinal protoplasm is interfered with it is obvious that other endocrine glands would become secondarily involved. Thus the terminal picture would be a pleuroglandular one. There are many conditioning factors. Myxedema is only one symptom of the hypothyroid state frequently a terminal one at that. The diagnosis of hypothyroidism should never rest on the presence of myxedema alone.

CHAIRMAN HOSKINS.—Hypothyroidism as I conceive it, is essentially two different conditions. One is marked by a general lethargy sluggishness of mentality and of metabolism. There is another type of hypothyroidism which, I think, is just as genuine an entity in which the picture is not one of lethargy but of irritability. This, I think, Dr Gordon might tell about.

DR. MURRAY B GORDON—There are two types of hypothyroidism in children. I take issue with Dr Shelton on the term "myxedema." There is a great deal of confusion in the literature as to the term "cretinism" in this country. Cretinism is used interchangeably to designate endemic cretinism and sporadic cretinism which some of us would rather call childhood myxedema. Cretinism is a condition due to endemic conditions and only partly due to hypothyroidism. As a result of a study of all the cases reported in this country I feel that so-called cretinism differs from that seen in Europe in that it is due to hypothyroidism and is not endemic. Some of these children with deficient thyroid activity have myxedema, and some have not. In suggesting the term "childhood myxedema" about fifteen years ago perhaps I was not correct in using the term for all the cases, but the original classification included both childhood myxedema and the hypothyroid state in children.

Hypothyroidism, or childhood myxedema, consists of two types: the first is the typical, fat, pudgy, lethargic child with myxedema or pitting of the skin; the second is the hyperexcitable child who is not fat and who does not present any myxedema. Both types have a low basal metabolic rate in addition to retarded carpal bone development, and both will show improvement following the administration of thyroid extract. You can compare the effects of thyroid extract in these two types of cases to the relationship between the effect of luminal and strychnine. A small dose of $\frac{1}{320}$ or $\frac{1}{40}$ gr. in the second type of child will have a sedative effect and as the dosage is gradually increased over a period of months a tolerance point will be reached, beyond which a large dose will produce hyperirritability. This latter dose depends upon the autogenous amount of thyroid extract present in the individual. These two conditions of myxedematous and nonmyxedematous hypothyroidism and the sedative and stimulative effects of thyroid extract must be considered in any discussion of the thyroid gland.

CHAIRMAN HOSKINS—I think the practicing physician is prone to overlook the fact that in the thyroid substance we have in effect, two drugs. It can have a pronounced anabolic effect, cause a child to grow as much as ten or twelve inches in a year, and serve as a general quieting agent; or it can be pushed hard and can become a "whip" agent. It happens unfortunately that thyroid is used largely for the whip effect when it is prescribed as a medicament for hypothyroidism.

DR HELMHOLZ.—Some of the cases to which Dr Gordon called attention have been diagnosed hyperthyroidism without exophthalmos because of the irritability

and the slight goiter, as it occurs in girls at about the age of puberty. We have seen a number of such cases that have come in as examples of hyperthyroids with basal rates of -24 to -30 .

CHAIRMAN HOSKINS—That group of patients is largely overlooked in general practice, and it is unfortunate because they respond to thyroid medication as well as the other type. It is rather curious that the irritable type of hypothyroidism has been so generally overlooked. In the classic report of the British Medical Commission in 1888, this aspect was strongly emphasized: the hypothyroid subjects studied showed all kinds of irritability, even to psychoses in some cases.

Dr Helmholtz mentioned the fact that the use of parathyroid—"parathormone"—the father of which sits at my right, leads not infrequently to a condition of refractoriness. The patient ceases to react to that preparation. I would be glad if Dr Collip would give us the rationale of why the material ceases to be active.

DR COLLIP—In the studies made during the past year in my laboratory on the various active principles of the anterior lobe of the pituitary, it was found that continuous treatment of experimental animals with certain hormones leads to the establishment of a state of nonresponsiveness on the part of the treated animal. It was shown that the blood of an animal resistant to the thyrotropic hormone was capable of neutralizing the effect of the thyrotropic hormone in a fresh test animal. Such results opened, so to speak, an absolutely new vista in endocrinology.

The point Dr Hoskins has made is important. It has been well known for a long period that an animal or patient treated with parathyroid extract known to be potent shows in a short time in some instances, and in other cases after a longer time, an apparent resistance to this hormone.

In the short time at my disposal I should like to say something about the principle of inverse response and the theory of antihormones and to make it clear that my recent pronouncements on these topics were of a theoretical nature. The theory had its birth in our laboratory, because of certain proved facts. This theory may be incorrect in many ways, but it is hoped that it will act as a stimulus to further work. The laboratory worker is often accused of being impractical, but here one may perhaps see a bridge from the laboratory to the clinic, since the antihormone theory can be applied quite as well in the clinic as in the laboratory. To be more specific, we found, with Dr Anderson, that animals treated for many days, weeks or months with an extract of the anterior pituitary lobe of the ox, pig, or sheep purified so that the active principle which has a specific stimulating effect upon the thyroid gland was being administered in concentrated form, showed in the first instance an elevation of the metabolic rate. In the course of a few days, however, the metabolic rate returned to normal, and as the experiment was continued the metabolic rate fell to -30 per cent of normal, which is the level of metabolism of the hypophysectomized animal. During the period of elevation of the basal metabolic rate, definite evidence of hyperplasia of the thyroid gland was obtained, but after the metabolic rate had fallen to subnormal values, the thyroid gland was diminished in size and quite comparable in its histologic appearance with the resting gland of the hypophysectomized animal. Here, then, we had what at first appeared to be a peculiar, if not ridiculous situation. The administration of a highly purified hormone extract, which one felt represented a very positive stimulant to the thyroid gland, actually produced, after a short period of definite stimulation—shown both by the elevation of the metabolic rate and by the histologic appearance of the thyroid gland—a state of hypothyroidism comparable to that seen in the hypophysectomized animal.

We found that the serum of these chronically treated animals resistant to the thyrotropic hormone was capable of neutralizing completely the thyrotropic hormone when the experiment was carried out on the most sensitive test object, the recently hypophysectomized rat. At first we were naturally inclined to think that we were probably dealing with an antigen antibody reaction, since the hormone extracts used contained protein. Other experiments, however which I cannot take time to describe, suggested the possibility that we were dealing with a true antihormone and the possibility had to be considered that the antihormone or antagonistic substance is present all the time, and that our experimental results could be explained on the assumption that we had raised the level of a substance which was already present in the blood. A theoretical concept which follows from this is somewhat as follows for each hormone there may be an antagonistic or antihormone and the stability of an individual as regards any particular endocrine aspect may depend upon the balance between the hormone and the respective antagonistic substance. One might even look upon this hormone antihormone complex as a 'buffer' system. In this way one might introduce a very definite quantitative aspect to the theory. It is not possible of course to detect the hormone and its antagonist simultaneously since one or the other must predominate.

CHAIRMAN HOSKINS.—The principle Dr Collip introduced, I think, is revolutionary. It is going to necessitate the rethinking of the subject matter of the whole field. Before, we had to deal, for instance, with only thyroid excess or thyroid deficiency but now we have had introduced the complexity of an antithyroid substance, apparently just as normal as the thyroid hormone itself. This finding materially complicates the philosophy of the situation.

There must have occurred to all of you the significance of this principle when it comes to practical therapy. If you put a baby on thyroid for example, and he promptly begins to develop antithyroid principle you are limited as to how far you can go. Perhaps Dr Collip will discuss the possibilities that lie before us in overcoming the handicap which the existence of antisubstances sets up. Personally I am inclined to believe Dr Collip has put his finger on the reason why so much gland therapy has been futile in the past.

DR. COLLIP.—If this work develops along the line it is pointing it is really a very serious bombshell thrown into endocrine therapy but it should not be entirely destructive. We should be able to treat patients much more rationally. To give an illustration, it is feasible that the case which you clinical men rightly diagnose as manifesting a hypofunctional state of A B or C gland is perfectly normal so far as the production of a particular hormone is concerned, but the trouble may be that there is too much of its antagonist. It may be that one gland produces both the positive substance and the negative substance, or it may be that the antagonistic hormone is produced somewhere else. But my point is that there is in the normal a balance between positive and negative in regard to individual hormones. If for instance you have a hyper antihormone state that state may be recognized by actual experimental demonstration of the antagonistic substance in the blood of the patient.

My plea is not that we give up treatment but that we study the patient from the standpoint of the hormone content so far as reliable methods are available. We have been experimenting along clinical lines with some of the pituitary fractions, which we know now produce in rats horses dogs, goats rabbits and guinea pigs a hyper antihormone state in these respective animals. Such extracts given to patients have led to similar results. We have been able to detect the antihormone for the thyrotropic substance in the blood of patients whom we have injected with this hormone. I may say the case which Dr A D Campbell demonstrated yesterday

day in his lecture actually has this antistubstance. It may be a good thing to produce a hyper antihormone state but let us find out whether we want to produce a hyper antihormone state or hyper hormone state before we start treatment.

The principle of inverse response is well illustrated if we compare a normal guinea pig with a normal rat. The guinea pig, as is well known, is highly sensitive to thyrotropic hormone of the anterior lobe. A small amount of this principle given to a guinea pig produces slight hyperplasia of the thyroid within a matter of hours, and after three days marked hyperplasia, together with a definite elevation in the metabolic rate, whereas the normal rat is practically insensitive to administered thyrotropic hormone. If you take the pituitary of the guinea pig and determine the amount of thyrotropic hormone in it, you will find it is very small, almost negligible. If you determine the amount of thyrotropic hormone in the pituitary of the rat, you will find that it is rich in this principle. I could go on giving other examples. Since the rat has a lot of thyrotropic hormone in its pituitary and is relatively insensitive to administered hormone, the principle of inverse response becomes evident—that is to say that the responsiveness of an individual to administered hormone varies inversely with the hormone content or production of the individual's own gland.

CHAIRMAN HOSKINS—That sounds like something new. Dr. Collip, I know, from personal conversation, recognizes the fact that this is something comparable to the old Weber-Fechner law we all had to learn in physiology. If 50 pounds of weight are resting on the back of your hand and you put an additional ounce on the pile, you feel no difference. However, if you have a 0.5 gram weight to start with and put on the same addition as before, you appreciate a very marked increase in the weight. The same principle, I think, holds here. If your patient is circulating hormone at a low level, the addition of a little more hormone makes a significant difference. If he has a lot there already—and especially if it is buffered by antihormone—the addition of a considerable amount more makes relatively little difference. This is extremely interesting as endocrine philosophy. I think this audience, however, will be more interested in what we know empirically as to how we can overcome this sort of handicap. Dr. Shelton, this principle that Dr. Collip has enunciated presumably has been operative during all the time you have been using practical gland therapy. How do you think you have circumvented it in the actual treatment of the patient?

DR. SHELTON—I don't know that we shall be able to circumvent it. There are several clinical arguments for the theory and several against it. In the first place, it is well known that some individuals with hypothyroidism or myxedema are very sensitive to desiccated thyroid administration. One may interpret this as meaning that those susceptible have few, if any, antibodies to this particular hormone. An individual with the thyroid gland surgically removed or otherwise destroyed is frequently susceptible to the hormone and may tolerate only a small dose of desiccated thyroid. Likewise I have seen normal individuals or so-called borderline patients who could take enormous doses of thyroid without elevation of the basal rate. In administering pituitary growth hormone, we have noticed that children seem to respond rapidly at first, then the response tends to continue on a plateau. Even when the dosage is augmented, the increase in weight and height does not keep up in direct ratio to the additional amount of the hormone introduced. However, we feel that perhaps this antibody effect may be circumvented by allowing a certain amount of time to elapse between periods of treatment. In other words we may learn that a period of treatment and a period of rest is better than continuous treatment.

One of the children we have had under treatment for two years grew 54 inches on the growth hormone, growth practically reached a plateau at the end of this time. While she was away in her home in Honolulu, without treatment she grew only 07 inch in thirteen months. Since she has returned, we have resumed administration of the pituitary fraction. She has grown approximately one inch in three months. I realize that the product we are using is an imperfect one perhaps containing the sex fraction and the thyrotropic and adrenotropic fractions as well as the growth. If our little patient has become refractory to any of these however, we are not aware of it. The fact remains that after a rest she has grown more on treatment during the past three months than she grew without treatment during the previous thirteen months.

CHAIRMAN HOSKINS—There is an old empiric rule that probably half an consciously has been based on this principle. It has been believed by shrewd practitioners that one gets better results on the whole by intermittent medication than by continuous medication. That always seemed a rather stupid sort of arrangement but I think we have here a rationale which makes it seem highly intelligent practice.

There will be other questions coming up in relation to the pituitary as the discussion proceeds. It is an important gland, perhaps the endocrine motor of the whole system. A baby cannot develop normally in utero without normal pituitary potations which he derives first from his mother and later from his own gland. He cannot go through infancy in a normal way without pituitary substance. He needs it through childhood and when he comes to the adolescent period, he is completely unable to make the normal transition without a functioning pituitary.

From the practical point of view the gland gets into every situation with which the pediatrician has to deal. Whether or not he recognizes its presence it is there as an important factor in the total life-situation of the baby—both physically and mentally—and probably as an important factor in personality. I hope that we shall have time to go back to some of these points.

Reference has been made in one or two places so far in the discussion to the parathyroid glands. Dr. McQuarrie has been thinking about these glands for some time, and I would be glad if he would take up the discussion at this point in relation to the practical aspects of the parathyroid as a contributor to welfare or ill fare."

DR. MCQUARRIE—I have been thinking about the parathyroids and the possible application of the theory in clinical conditions showing disturbances in the functions of the glands, namely, in the states of hypofunction and hyperfunction. We encounter idiopathic parathyroid tetany frequently, and, while the condition is not common, every one has had some experience with such cases as well as with infantile tetany which might be related. During recent years many cases have been encountered some of them in children, of hyperfunction of the glands due to tumor in some instances, or to glandular hyperplasia in others.

I have wondered, since hearing Dr. Collip's paper in New York before the Federated Society a few months ago, whether our cases of idiopathic parathyroid tetany may not in some instances be due to overproduction of some antistubstance. Again in the hyperparathyroid cases with hyperplasia, do they represent one phase in the reaction to this mechanism? Have some of the hypoactive cases gone through a hyperactive phase? We have all sorts of possibilities before us in the light of this new work.

Just as we have diabetogenic and thyrotropic substances in the anterior lobe, Hertz and Krancs, of Boston, have recently discovered a parathyrotropic substance a substance which when injected into animals produces very definite hyperplasia of

the parathyroid glands, that is, an increase in the number of parathyroid cells, enlargement of these cells, and probably hyperfunction as well.

While any clinical applications will be experimental for a long time, in one of our patients with so called idiopathic parathyroid tetany, we have injected daily for a week at a time some anterior lobe extracts already available to us in the hope that these might possibly contain some of the parathyrotropic substances which would tend to have a stimulating effect in such patients. Since the first experiment was not entirely satisfactory, we are repeating it the second time. The first study has shown that the calcium and phosphorus excretions are increased as they are in hyperparathyroidism. The calcium and phosphorus of the blood have not so far responded as one expects them to on administration of the parathormone or in the presence of hyperactivity in the case of tumor or of hyperplasia of the gland, but it is suggestive and certainly our approach to the subject seems justifiable in the light of Dr. Collip's new hypothesis.

I would like to say in connection with this that refractoriness or immunity which is produced in hypoparathyroid patients when they receive the parathormone over a long period of time may be due to one of several factors which one could correct or avoid. In addition to the occasional interruption of therapy already referred to, the factor of dosage is very important. It is remarkable how sensitive these individuals are to small doses of parathyroid substance, at least at the beginning. This fits in well with Dr. Collip's theory, I think. Minimal effective dosages should be established for each case and then adhered to. Diet is another factor in this particular disturbance at least. When the patient is getting a high calcium and phosphorus diet, less hormone is required. The ratio of the calcium to the phosphorus in the diet, the total base and acid in the diet, and the hydrogen ion concentration or acid base equilibrium in the body fluids, influence the activity of the gland very much. These factors certainly should be taken into consideration. We should do everything we can with vitamin D, the acid base balance and high calcium in the diet without depending entirely upon the parathyroid extract. Then, by giving the patient small doses from time to time, we can at least extend the period of usefulness of that hormone.

The child who has hypofunction of the parathyroid certainly is an irritable individual. Whether this condition is due to increased brain cell membrane permeability or to some other fundamental disturbance in cellular physiology, he is very irritable and shows increased muscular tonus. According to some recent work, there is an increase of water contained in the brain tissue in the state of hypoparathyroidism. Under such conditions the cortical cells perhaps behave abnormally, as do the other cells of the body.

In the hyperparathyroid state the individual is less responsive. There is a lessened neuromuscular irritability. He is hypotonic. He may be irritable from pains in the bone due to tumor growth or cyst formation and to some changes in the muscles, but he is not hyperirritable in the sense that the hypoparathyroid patient is. I can say, from the personality side, therefore, that this change in physiologic state makes a basis for disturbances in personality reaction. Mental reactions beyond that I know nothing about. You know so much more concerning this aspect of the problem that I wish you would tell us about it.

CHAIRMAN HOSKINS—May I ask Dr. Collip to interrupt Dr. McQuarrie. What is there in this idea that, as we give parathormone with a hypodermic needle, we are a long way from imitating the way nature gives it to the patient? We give at a single dose what may amount to several hours' normal supply. When this is used up, the patient sinks into a trough of total deprivation. Then we give him another "bump." Possibly all the peaks in the dosage stimulate the production

of the antisuistance I should like to know what Dr Collip thinks of this. In stead of setting up this 'up-and-down' situation, we should try as nearly as feasible to carry the patient along on a plateau of dosage and at as low a level as will suffice

DR. COLLIP—The more frequently an extract is administered and the smaller the individual dose, the nearer you are approaching ideal conditions. But, of course, there are obvious limits to this. One would like to know for instance, if this were carried out as far as possible, whether by the reduction of dosage and by the increase in the frequency of injections, this antihormone response would be avoided. In nature the absolutely normal individual's various glands are pouring out hormones continuously at a certain definite rate. It may be normal for one species of animal to have a slight predominance of the antisuistance whereas another has a predominance of the positive. I have no absolute proof of this but I feel that the reason a dozen dogs can be killed with the amount of parathyroid extract one rabbit will thrive upon is a good illustration of this principle.

CHAIRMAN HOSKINS—I think we have to assume this mechanism is not put in just to make trouble for the endocrinologist. But it is sound as furnishing a lead at any rate to try to deduce what the ultimate significance of the mechanism is in the evolutionary process. We shall have to assume at this stage that it is a protective device to prevent the individual from overdosing himself with his own hormone under the vicissitudes of life. We shall also have to assume that there is a balance, ordinarily, so that this regulating mechanism does not defeat its own purpose. A governor on an engine that shuts off steam when you want the engine to be pumping would be a poor sort of governor.

It is necessary to assume that the antisuistance comes on only when the hormone rises for some special reason too high and has to be corrected so to speak. An important aspect sometimes overlooked is the fact that the individual is not just a collection of adrenals and thyroids and stomachs and colons and things of that sort but a person with the personality that gives this 'mess of viscera' its meaning. That topic, I think, could be touched upon with profit by Dr McQuarrie. He told about the tendency to tetany which is very interesting as physiology but what about these conditions in relation to personality? What difference does it make to the personality of the youngster? How much more does the mother have to stay up nights with him because of his parathyroids? The influence it has on personality is the most important part of endocrinology. Unfortunately we have been rather extensively indoctrinated on the "influence of glands on personality" but the doctrine is sadly lacking in factual support. Nevertheless, despite the abuse the topic has had at the hands of reportorial scientists, it is still an important topic.

There is one gland which, according to Riddle, probably dates back in importance to the preterrestrial stage of our ancestral history—which has permitted us to gather for this delightful occasion today and without which our ancestors would have perished from the earth—a gland which has been a paradox, especially to pediatricists. I am referring to the thymus gland, the subject of Dr Graeme Mitchell's talk.

DR MITCHELL—While the subject of endocrines should, because of the interrelationship of the various secretions, be considered together, there are individual interests concerning each of the so-called glands of internal secretion. In approaching the subject of the thymus gland, I wish to make clear that I am interested in it as a clinician who is faced daily with the attempt to solve the problem as to what should be done in instances in which this organ possibly, either by pressure or by some other mechanism causes symptoms.

Opinions concerning the thymus have, like the pendulum, swung from one end of the arc to the other. Recently some pediatricists, whose opinions must be regarded with respect, have intimated that the thymus gland never causes symptoms. In such a controversy it would appear from a philosophic point of view that the truth might lie somewhere between the extremes.

The literature on this subject is cluttered with a good deal of material based upon erroneous or unjustifiable presumptions regarding the pathology, physiology and functions of the thymus gland. Those who have studied the subject experimentally by observations on animals after the thymus has been removed or by injecting extracts of it into animals have often urged opposing opinions. There arises, too, the difficulty of translating to the human the results of experiments on animals since it is possible that the organ may have different functions in different species.

I have made a mathematical analysis of a group of patients, some of whom had enlargement of the thymus gland according to roentgenographic interpretation.

For example, 197 patients could be divided into four groups. Eighty patients had enlarged thymus and symptoms, 36 had enlarged thymus but no symptoms, 43 patients had no enlargement of the thymus but did have symptoms which are often attributed to the thymus gland, and last, there was a comparative group of 38 patients without enlargement of the thymus gland and without symptoms. This allowed analysis by means of the fourfold table and gave a sigma of 2.26—the mathematical implication being that these four groups come from the same universe or, in other words, that the symptoms mentioned (stridor, cyanosis, and convulsions) were not inevitably associated with enlarged thymus.

If these 197 patients were divided into two groups, it was found that 116 had enlarged thymus according to the roentgenograms and eighty one did not. Of the former group, 69 per cent had symptoms, and of the latter group, 53 per cent. Applying the chi square test the sigma was 6.39—that is, these two groups had not come from the same universe, and the symptoms mentioned, therefore, are more likely to be associated with enlarged thymus.

Of 80 patients who had enlarged thymus, there were 56 who had complicating conditions (congenital heart disease, respiratory infection, and increased intracranial pressure) which might equally well have been responsible for the symptoms. That is to say, there were only 24 patients in whom some other cause could not be discovered for the symptoms. Applying statistical analysis to these two groups it was found that the sigma was 4.47 and that the ratio of incidence of symptoms was higher in patients with enlarged thymus who had other reasons for these symptoms than in those patients who had only enlarged thymus. The implication here is that a child with an enlarged thymus and some complicating condition such as those mentioned is more liable to have symptoms than one with an enlarged thymus only.

It is interesting that of 116 patients with enlarged thymus 20 had pylorospasm, whereas, of 81 patients without enlarged thymus 33 had pylorospasm. That is, from a statistical viewpoint, there is no obvious association between enlarged thymus and pylorospasm.

CHAIRMAN HOSKINS—May I interrupt Dr. Mitchell to extend my heartiest congratulations to him for having brought into his work an accurate calculation of probability. We deal with things in medicine all the time which are probably true or probably not true. There are a great many open questions. I think it is a definite advance that we are beginning to calculate as accurately as can be done just what the odds are that a given assumption is true and what the odds are

against it. We can judge better if we know the odds are, for instance 20 to 1 in favor of the assumption than if we know only that there is some probability that it is true.

What do you think, Dr. Mitchell, of the remarkable work on the thymus that has recently been reported from Philadelphia?

DR. MITCHELL.—Dr. Hoskins previously called my attention to the recent work of Dr. Bowntree in which there was remarkable accelerated growth and development in rats injected intraperitoneally by a thymus extract made by Hanson. If continuation of this work properly controlled bears out the original observations, much significance can be attached to it.

CHAIRMAN HOSKINS.—We have been giving extracts to rats for a great many years, and nothing has ever before been seen like a rat being weaned at three days of age or giving birth to young at forty two days of age. Such precocity is as startling as would be that of a little five-year old girl giving birth to twins. That sort of thing is out of the biologic picture as we have known it before. Dr. Bowntree's pictures are convincing in that rats four days old were seen running around with coats of fur while normal rats raised under the same conditions but without the thymus extract could only waddle awkwardly about as little pink blobs.

DR. MITCHELL.—I am going to recite to you certain viewpoints rather than conclusions, which summarize my present views on the thymus. It appears that some of these statements can be made with a reasonable amount of assurance.

In some instances an enlarged thymus gland can cause pressure upon the structure in the thoracic inlet and lead to development of such symptoms as dyspnea, suffocative attacks, crowing respirations, cough, and cyanosis. The symptoms mentioned occur with many other diseases and abnormal conditions and these are perhaps more frequent causes of all of them than is an enlargement of the thymus.

An infant or child who has some cause for dyspnea, cough, and cyanosis, such as an infection of the respiratory tract, congenital heart disease, and the like, and who also has an enlargement of the thymus gland is more liable to develop these symptoms. Probably the enlarged thymus may aid in their production, but in some instances it would be a factor which would be insufficient in itself to cause such symptoms.

From a statistical point of view there is no significant association between an enlarged thymus and pylorospasm.

There is no proof that convulsions are associated with an enlargement of the thymus gland and the presence of convulsions even in a patient with an enlarged thymus gland should lead to a suspicion that there may be increased intracranial pressure, spasmodophilia (tetany), or some other cause.

An enlarged thymus gland according to roentgenograms is by no means necessarily associated with symptoms.

Even when symptoms of obstruction are present in an infant or child with an enlarged thymus, search should be made for other possible causes.

I have no solution to the question of the relationship of sudden death when not explicable by some discoverable cause, to status thymicus lymphaticus.

CHAIRMAN HOSKINS.—Dr. Riddle called our attention to his belief in the importance of our ancestral thymus gland. If a few million years ago it had gone out of the picture we should not have come into existence. There is another gland the function of which is such that if it had not appeared in our individual pictures about the time we drew our first breath we again should not be here. I have asked

Dr Gordon to talk to us about the adrenal gland and its relation to practical pediatrics, and perhaps to touch upon its function in getting us past the intrauterine course of existence into the postnatal phase

DR GORDON—Before going on to the discussion of the adrenals, I would like to speak about the thymus. The question of the physical condition of the thymus must be absolutely differentiated from the endocrine aspect. We feel that there is no definite physical knowledge as to the size of the thymus at various ages in infancy and even at the same age in various children. It tends to be larger in stout, well developed children and smaller in the undernourished and thin. Information as to the size of the thymus by means of x-ray pictures may not always be exact, as the shadow is larger during inspiration than during expiration, the stage of respiration in which the picture was taken is, therefore, of vast importance in judging the size of the gland. Fluoroscopic examination offers more information than one isolated x-ray plate. One of the important steps in interpretation of signs and symptoms of thymic enlargement is standardization of the methods used in making roentgenograms of the gland—Pancoast's work should be studied by every one interested in this part of the subject. As to the endocrine aspects—most of us had dropped the thymus as a gland of internal secretion, but the recent work of Rowntree, Jaffe, and others may bring it back into endocrinology. In connection with the effects of thymic extract, I wish to refer to the limited experience that I have had with thymocrescin in two cases of anterior pituitary deficiency of growth. The patients were both boys, one seven and the other seventeen years old. We were unable to observe any effects on the height in either one after several months of treatment. It is probably unfair to judge the effects of the extract in the older boy as his epiphyses were almost united.

There are several aspects of the adrenal which I should like to discuss. The first is the part which the adrenal gland plays in the transition from prenatal to postnatal changes especially in respiration. It has been known for some time that the adrenal gland is very large before birth and that this increased size is due to the large adrenal cortex. Immediately after birth there is a degenerative change taking place in the adrenal cortex, this process goes on rapidly for the first week and then at a lower speed for the first year. It takes about two years before the medulla is absolutely differentiated, so that the conditions in antenatal are entirely different from postnatal life. We also know that in antenatal life there is a low oxygen tension, a low oxygen saturation of the blood, and that in spite of this the utilization of the blood by the fetus is much greater than by the mother. Animal experiments have shown that the responsible factor is the adrenal cortex. We cannot go now into what these animal experiments have been, but it seems that the size of the adrenal cortex is an indication of the effect of the adrenal gland upon tissue respiration and that, upon the birth of the child with the intake of a large amount of oxygen and the increase in oxygen tension, the adrenal cortex degenerates. This demonstrates that a large adrenal cortex is not necessary after the onset of pulmonary respiration.

Anything which would interfere with the normal interchange of oxygen should show a persistence of fetal conditions. This has been demonstrated clinically in two conditions. Dr Goldzieher found at autopsy an absence of adrenal cortical involution in three cases of transposition of the great vessels with septum defect and marked cyanosis in infants of an age at which involution should already have occurred. Goldzieher and I found that an increased respiratory rate is so prominent a symptom in adrenal hemorrhage of the newborn that we suggest the term "psendopneumonia of the newborn" for this condition. This is due to an attempt of a damaged adrenal cortex to adapt itself to the new conditions present at birth.

The diagnosis of adrenal hemorrhage is difficult and we found that only eleven cases have been diagnosed during life out of the eighty-one in the literature. Goldzieher and I have advanced the following syndrome of adrenal hemorrhage in the newborn with two groups of symptoms—those due to acute adrenal insufficiency and those produced by internal hemorrhage. The symptoms of acute adrenal insufficiency are: The infant presents the appearance of pneumonia without any physical or x-ray evidence. There are present increased respiratory rate, hyperpyrexia, cyanosis, purpuric or petechial spots, and certain definite chemical changes in the blood, the principal ones being hypoglycemia and an increase in nitrogen metabolites. The symptoms of the nonendocrine elements are those of any internal hemorrhage such as shock, collapse, weak and irregular pulse, cold extremities, air hunger, and increasing pallor. These are especially marked if the hemorrhage is extensive and may overshadow the symptoms of adrenal insufficiency. The abdomen is doughy to the touch, and there may be a palpable tumor in one or both kidney regions.

Either set of symptoms may predominate and give the different types of pictures which have been reported. For instance, Arnold reported his case from the view point of an internal hemorrhage alone while others have reported from the view point of acute adrenal insufficiency.

Adrenal hemorrhage may occur in other conditions in later life as in the course of acute infections and may present the same set of symptoms as found in the newborn except that the respiratory rate is not as greatly increased.

The next condition of importance is that of acute adrenal insufficiency. There seems to be a lack of appreciation in the literature as to the difference between acute adrenal insufficiency as exemplified in adrenal hemorrhage and chronic adrenal insufficiency as exemplified in Addison's disease. In one we find an acute process taking place rapidly and in the other we find a condition which has appeared over a number of years in older children in whom there have been metabolic alterations especially to other glands of internal secretion, where the two pictures are entirely different. In acute adrenal insufficiency there are the same symptoms as in hypoglycemia, high nitrogen metabolites, and perhaps an increase in respiratory rate and high temperature. In chronic insufficiency the picture is really one of Addison's disease with a history of tuberculosis in either the patient or his family. Bell has recently shown that an x-ray diagnosis of the latter may be based on the presence of calcified glands in the region of the adrenal gland.

In acute adrenal insufficiency as in adrenal hemorrhage we have advised treatment from three approaches: first, the administration of a potent adrenal cortical extract such as cortin, interrennin, eschatin; second, the administration of large amounts of sugar either by intravenous injection or by hypodermoclysis; third, blood transfusion of an adequate amount. In chronic adrenal insufficiency the administration of a potent cortical extract is important as shown by Rowntree. The use of glycerin extracts by mouth as advocated by Hoskins and Freeman may be of some benefit, as will the ingestion of food with sufficient vitamin content.

The adrenal gland seems to have a definite influence on sex. It has been shown but not definitely proved that hyperplasia of the adrenal cortex during fetal life results in pseudohermaphroditism. Hyperplasia or neoplasia of the adrenal cortex during infancy or childhood produces precocious puberty. We were able to report a few years ago the fifth case in the literature of this condition as it occurred in a boy three and one-half years old. It is much more common in girls. Another type found in females between the ages of thirty-five and fifty years and known as "virilism," is due to a neoplasm or hyperplasia of the adrenal cortex. In this condition, characterized by a tendency toward heterosexual changes, the individual

takes on the appearance of the male sex as evidenced by an increase in hair growth resembling that of the male, a change in voice, and perhaps even a change in psychic

It is sometimes difficult to differentiate between obesity due to hyperadrenalism and that due to hypopituitarism. Lately the literature concerning instances of adrenal obesity in infants and children has increased. These children may show hypertension, hirsutism, and perhaps signs of precocious puberty and heterosexuality.

An increased activity of the adrenal cortex will be accompanied by an increased osseous development as shown by x-ray examination, especially in the wrist. We have not been able to find any references to gigantism caused by overactivity of the adrenal gland. On the other hand, there is a condition known as progeria which is supposed to be accompanied by hypoplasia of the thymus, adrenal, and pituitary and is characterized by a marked infantilism and a senile facies.

CHAIRMAN HOSKINS—I want to call to your attention the fact that one of the most difficult problems confronting the clinical endocrinologist is that of the relationship between the thyroid and pituitary. There is a group of clinical pictures in which it is not easy to decide whether the thyroid or the pituitary is at fault or whether both glands are coincidentally involved. Dr. Shelton will tell us something about the practical management of this very difficult question, how the distinction is made, and what can be done therapeutically.

DR. SHELTON—I am not sure that I can tell you how to distinguish between these disorders, but after considerable study of osseous unfolding, we feel we have devised a method which is at least informative.

Dr. Gordon spoke about the advance in carpal development in children with hyperactivity of the adrenal cortex. We know that children grow in height and develop structurally at a rather definite rate. It has been shown by a number of observers that removal of the thyroid anlage in tadpoles retards metamorphosis into the frog. These tadpoles may be kept in the tadpole or embryo stage of development indefinitely. If fed thyroid or if a piece of thyroid tissue is later grafted under the skin, this tadpole will metamorphose and develop into a frog. Therefore, the thyroid hormone has much to do with tissue differentiation or tissue unfolding. We feel also that there is a remarkable difference between development as we know development and growth of the organism *per se*.

Most of the dwarfs whom we have been treating (considered as having a primary pituitary etiology) show normal or only slightly retarded bony development, while hypothyroid dwarfs and those not markedly under stature but presenting evidence of hypothyroidism show a very marked retardation in osseous development (unfolding). So I feel that the clinical differentiation, particularly by the roentgen ray, may rest on this point: namely, if the child is of fair to good height or even dwarfish and if coincident with this there is a markedly retarded osseous development, as evidenced by retarded carpal or other bony unfolding, the primary and essential difficulty is probably due to a deficiency of thyroid secretion. If, on the other hand, I find a child who shows little evidence of retardation or unfolding of somatic development and yet is small or dwarfish in stature, I feel that the thyroid is not seriously involved and look to the pituitary to be primarily at fault. As regards overgrowth or speeding up of development, I think I can say safely that hyperthyroidism will produce rapid osseous unfolding. I feel that anything which will speed up development in general, and by development I do not mean growth but only actual tissue differentiation or metamorphosis, will ultimately be reflected in the framework or the somatic make-up of the individual. Since pituitary ablation results in thyroid and adrenal cortex atrophy, and thyroid ablation results in a generalized slowing up of all body processes—including the pituitary—it is likely that

in every child suffering from abnormal deviation in stature or aberrant development, the etiology is complicated. In a sense all are pleuriglandular. It frequently becomes necessary, however particularly for the sake of treatment to ascertain the primary and paramount difficulty. There are many clinical points of dissimilarity, but to me, at least, the roentgenogram of the bony framework is the most informative.

CHAIRMAN HOSKINS.—Dr Shelton will you take this question that was submitted from the audience? 'Is the pharmacentic claim correct that thyroid extract is the only gland product that can be given by mouth and produce any effect?'

DR SHELTON—This is a difficult question and I can answer it only in the light of my own experience. Many men of equal experience may have different views. The only purely endocrine preparation that I use by mouth in children is thyroid. Adrenalin and some ovarian preparations and placental preparations including emmenin, when given in large doses, have been shown to produce a moderate therapeutic effect. Dr Hoskins has shown that large doses of a glycerine extract of adrenal cortex by mouth will increase the blood pressure in his schizophrenic patients from 15 to 25 mm of mercury. I do not believe he has been able to produce this effect in a series of normal controls. Personally I have given large doses of pituitary preparations by mouth over prolonged periods without ever having convinced myself that they had any therapeutic effect. It has seemed to make no difference whether the preparation was coated or not. These were controlled observations in which no other gland product was given. Many pharmacoeutic houses make tablets containing various glandular preparations plus a little thyroid. These frequently produce certain beneficial effects, but it is quite likely the thyroid which does the work. In my estimation one should never give thyroid in combination with other preparations. If you suspect the patient of needing thyroid, give him thyroid alone. Other things may be added if desired for an experimental clinical test after the effect of the thyroid is measured. For the present at least it appears best to limit the administration of gland products by mouth in children to desiccated thyroid.

FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CLEVELAND JUNE 11 AND 12 1934

Round Table Conference on Adolescence

Leader Dr Borden S Veeder St Louis

Assistant Dr Sidney I Schwab St Louis

The Chairman opened the meeting with a discussion of some of the physical problems of puberty and adolescence. The variations in the chronologic development of the accelerated growth cycle of this period were pointed out and the failure of physical growth to parallel the age in years. The importance of skeletal age was emphasized. The development of medical problems on the basis of the unorganized growth was discussed and also the tendency to fatigue and overstrain which accompanies it.

Dr Sidney I. Schwab (St Louis) continued the introductory remarks with a discussion of some of the psychologic phenomena of the period. The importance of

the adolescent as a social unit, the development of personal identity and awareness on the part of the adolescent, and the changing character of his thinking from conceptional to abstract were among these phenomena. As an approach to the subject, adolescence may be regarded as a final preparation to reach a social adjustment, and the failure to make this adjustment, as a result of innate constitutional characteristics, faulty training or environmental obstacles, leads to the adolescent problems and conflicts. In the study of the adolescent three things must be considered: the adolescent as a physical being with his growth and development, the adolescent as he behaves and reacts to his particular environment, and third, the content of his consciousness.

Dr Harold C. Stuart (Boston) spoke of the necessity of restudying adolescents from the standpoint of metabolism, activity, sleep, diet, etc., on the basis of the individual spurt of growth rather than by chronologic age periods as has been done in the past.

The question of distinguishing simple problems, which should be handled by the pediatrician rather than the psychiatrist, from deeper problems potentially psychiatric in nature, was discussed by the Chairman, Dr Schwab, Dr Alvah Newcomb (Chicago), Dr Stuart, Dr Bert I. Beverly (Chicago), and Dr George F. Munns (Winnetka, Ill.). Several illustrations of these differences were presented. It was agreed that this was largely a matter of medical education and necessitated emphasizing the importance of regarding the adolescent as an individual rather than a purely physical mechanism. The importance of early training as a matter of prevention was stressed, and hence the work of the pediatrician was of paramount importance. The danger of referring all behavior problems and difficulties to the clinical psychologist as an easy way for the pediatrician to sidestep his problems was brought out in the discussion.

Dr Beverly brought up and discussed the difficult problem of the child who had the physical development of the fourteen year old, the mental development of the twelve year old, and with this the emotional control of a still younger child. The Chairman felt there was little value in trying to hasten puberty by hormones unless there was definite endocrine disturbance. It was pointed out by Dr Charles Schott (Chicago) that it is best to widen out the activities of the child with superior intelligence and keep him with his physical age group. The question of "emotional maturity" in this connection was discussed by Dr Schwab, Dr Beverly, and the Chairman.

Health Education—Sex Education—The point was stressed by the Chairman that health education before puberty was chiefly the formation of routine health habits. In early adolescence more formalized instruction in hygiene was possible. Sex education should not be overstressed but should fit into this course in hygiene. Dr Schwab, Dr Oliver Hill (Knoxville), Dr G. F. Munns, Dr S. J. Crumrine (New York City), Dr I. H. Trumpeier (Chicago), Dr W. B. McIlwaine (Petersburg, Va.), Dr C. Harvey (Pontiac, Mich.), Dr C. Schott (Chicago), Dr E. H. Schorer (Kansas City), and Dr Beverly took part in a general discussion of sex education. Considerable difference of opinion developed as to the relative function of the parent and the school. There was general agreement as to the danger of overemphasis of sex education by propagandists.

Overstrain and Physical Breakdown—The question was raised as to the cause of the frequent breakdowns during adolescence. The Chairman stated he considered the complexity of modern life to be the chief factor. Individuals who lacked stamina on a constitutional basis tried to carry too heavy a load. Dr Harvey stressed the educational problem with the college demands, as a most important factor. Dr G. M. Lyon (Huntington, W. Va.) and Dr Schwab emphasized the factor of parents.

setting too high goals for many children, which made unreasonable demands upon them. There was need for a much sharper differentiation of adolescents who were attempting to enter on professional careers. Dr Forbes (Denver) and Dr E. T. McEnery (Chicago) discussed the importance and frequency of tuberculosis as a cause of the breakdown at this period.

Physical Exercise and Athletics.—Dr Alvah Newcomb raised the question of the dangers of overexercise and certain sports to the child of this period. The Chairman stated that he felt that this was one of the most important points to be considered and referred to the dangers of excessive competitive exercise. Frequently the importance of the school team was placed before the welfare of the individual boy. Too much competitive sport with continuous training was bad. He considered that there was decided need for better medical supervision of athletics in the schools and referred to the frequency with which the boy needing exercise and athletics was put to one side while the natural athlete was given the entire supervision and training. Dr Lyon spoke in particular of the dangers of basket ball. He referred to the tournaments held by the colleges for preparatory and high school boys in which four or five competitive games were played in the course of two or three days. Usually there is no medical supervision of such teams. Dr Munns felt that track sports and basket ball were the most dangerous forms of adolescent sports unless they were most carefully supervised. Dr Munns referred to the present attitude of many parents in recent years as being in agreement with the views being expressed at the Round Table. Dr Oliver Hill (Knoxville) called attention to the danger of prohibiting sports and exercise to certain boys, as it made them stand out as exceptions and produced a bad psychologic effect upon the individual boy. Dr Newcomb referred to the work of the Boy Scouts which he felt was in need of very much medical supervision. Dr Schwab spoke of the wrong selection of sports for boys. Some boys are forced by their coaches or schools to take part in games in which they are not interested or may even dislike. The Chairman spoke of the problem of the nonathletic boy who has a secret longing or desire to be an athlete and because of his physical inability or lack of aptitude takes a contemptuous attitude toward sport as a defensive mechanism.

NOTE.—Owing to the informal nature of the discussion at this Round Table it was necessary either to publish the entire proceedings of the two conferences or briefly to abstract the points discussed in a very general way. As the first method would require some sixty printed pages, the second method was adopted.

CONFERENCE OF REGION I OF THE AMERICAN ACADEMY OF PEDIATRICS AND THE TRI-CITY PEDIATRIC GROUPS

Region I of the Academy and the Tri City Pediatric Groups (the New England Pediatric Society, Philadelphia Pediatric Society, and the Section of Pediatrics of the New York Academy of Medicine) met in a joint conference Oct 19 and 20, 1934, at the New York Hospital—Cornell Medical Centre—and the Ambassador Hotel, New York City

REPORT OF REGION I

December 1, 1934

To the Executive Committee of the Academy of Pediatrics

The Chairman of Region I begs leave to submit the following report of this date, covering the period since June of this year

The membership of Region I, which now includes the eastern provinces of Canada, now totals 236

For purposes of record it is to be noted that Dr Edmund R McCluskey has been appointed cochairman for Pennsylvania, Dr Edward J Wynkoop, cochairman for New York, Dr William P Buffum has succeeded Dr Henry E Utter as chairman for Rhode Island, and Dr Alton Goldbloom has been appointed chairman for the eastern provinces of Canada

The first regional conference was held in New York City on October 19 and 20. A program was carried out and is believed to be the precursor of an annual series which will stimulate interest in the Academy and prove an excellent means of getting the members together

Between sessions a special meeting of the combined regional committeemen and the state chairmen was held with President Cooloy and Dr Grulee as guests

Dr Grulee opened the meeting with a discussion of the plans being made for the national meeting which is to be held in New York City next spring. He asked the active interest and support of all members in the East, spoke of the desirability of continuing Panel and Round Table Discussions, and outlined the plans for the meeting in their tentative form

Maine—Dr Foster spoke of the difficulties of having a broad state program in the less densely populated states where so few men in the state were members and said he felt it would be desirable to have more explicit knowledge of what the Academy felt was a sensible program for such a state as Maine

Dr Grulee in discussion said that the first thing every Academy member should ask himself was, "How can I help?" He then spoke at some length of how different states had carried on activities, illustrating his point by examples of what has been done in certain states, and advised a careful reading of all reports of Academy activities in the *JOURNAL OF PEDIATRICS*

Vermont—Dr Johnson reported that there had been an increased interest developed in diphtheria immunization and suggested that the Academy should take a much more active interest in the matter of radio advertisements concerning the welfare of children, as not infrequently the advertisements overstepped the bounds of truth

New York—Dr Laws expressed the belief that each state must necessarily encounter different problems and that in the southern end of New York it is hoped

to place Academy men in positions of responsibility, whether in local pediatric societies or child welfare movements.

Maryland.—Dr Smith spoke of certain difficulties in solidifying the work of the Academy. He felt confident that there will be a steady and sure growth.

New Jersey.—Dr Nichols reported that many ways of putting Academy members to work have been found. A continued drive for diphtheria immunizations is still on. An attempt to secure more Mantoux tests is being evolved. The supervision of various programs of child welfare agencies is offered. A program of postgraduate teaching for general practitioners continues, and a program for the location of malnourished and neglected children has started with the objective of having a larger participation by both general practitioners and pediatricians. A gratifying increase in the membership in New Jersey was also noted.

Delaware.—Dr Handy said that an attempt to secure better cooperation between agencies interested in the welfare of children was under way.

Connecticut.—Dr Dunham said that there had been several meetings in which the importance of the Academy to the pediatricians of the state was emphasized.

Pennsylvania.—Dr Stokes reported that the Academy members were taking an increased interest in all the problems concerned with children. There is still a great need for more education for physicians in the rural districts and plans were being made to make this possible.

Quebec.—Dr Goldbloom spoke of the many difficulties inherent in the pediatric situation. The chief of these is the division of the population into two distinct groups, French, and English. Not only is there no association between the ordinary population, but the medical groups themselves are as far apart as though they lived in different countries.

Rhode Island.—Dr Buffum reported that the activities of the members have been in association with other pediatricists, as a result of this there has been a clearer understanding of what should be attempted. One outcome has been that all children entering school for the first time were examined, one-third of whom were examined by their own physicians.

The next business discussed was the meeting place for the Regional Conference next year. Philadelphia was chosen the time to be decided by the Philadelphia group. The type of program was considered at some length but no final decision was reached, it being felt that this should be left to the local committee.

The only recommendations that the Regional Committee makes to the Executive Committee are first, that the wisdom of putting stars before the founders' names in the roster of members is questioned, and, second, that the Pennsylvania members do not believe that it will be wise to increase the dues at present.

The Chairman of Region I believes that there has been a steady growth of interest in the Academy in the East. This has been evidenced by many more applications for memberships, many more inquiries, and an attendance at the regional conference in New York City far exceeding anything that was expected. This increase in interest makes it very evident that along certain lines the Academy must plan much more definitely to define its work rather than to amplify it. It is believed that it is the part of wisdom to advocate the following proceedings:

1. It shall be required that all state chairmen report each year to the Regional Chairman on a blank to be drawn up by the Executive Committee.

2. Each state shall be required to have at least one yearly meeting which could easily be arranged to take place at the state society meeting. This is now voluntary but should be made obligatory.

3 The regional committeemen shall be asked to widen their activities beyond the mere supervision of application blanks. Each regional committeeman might be made responsible for the activities of the Academy in two or more states, both by conference with the state chairmen and attendance at various state meetings or conferences. In all cases in which objections are made to candidates, the regional committeeman for the district in which the question arises shall be asked to render a decision rather than the regional chairman.

4 It is believed to be a good policy to ask the Executive Secretary to furnish the Children's Bureau in Washington with a list of the members of the Academy and to request that all publications of the Bureau be sent to the members. This list should be kept up to date.

It is with regret that I announce the resignation of Dr. Ethel Dunham as chairman for Connecticut.

Respectfully submitted,

LOUIS C. SCHROEDER, M.D.

The program included the following papers, the abstracts of some of which are given:

October 19 at the Ambassador Hotel

Hypoparathyroidism. Arthur F. Anderson, M.D.

A diagnosis of hypoparathyroidism was made in this case because of the symptoms of stiffness of the extremities, increasing restlessness, persistent vomiting and headache, with the finding of a low blood calcium. The patient was a nine year old female white child. After the administration of parathyroid hormone, the calcium values in the blood rose, and the symptoms disappeared. She also received viosterol and thyroid extract.

Hyperteleorism. Louis Weymuller, M.D.

A white male child, nine years old, was presented as a case of hyperteleorism. The skull was wide laterally and flat in the occiput, the vault of the head being enlarged considerably beyond normal size. There was a large, high forehead with prominent frontal eminences. The eyes showed the usual appearance. The condition is essentially a developmental anomaly of the sphenoid bone of which there is an excessive growth of the lesser wings.

Third Ventriculectomy as the Rational Treatment of Obstructive Hydrocephalus John E. Scarff, M.D.

In this child who presented an extremely advanced case of hydrocephalus, the process seems to have been arrested by a procedure which carries with it a very low surgical mortality. It is unfortunate that the disease was so far advanced when the child was operated upon, but there is reason to believe that a similar procedure carried out in earlier cases could save many children for a useful and normal existence.

The treatment of nonobstructive (or communicating) hydrocephalus by the "closed" method, cauterization of the choroid plexuses through a "ventriculectomy" without removal of the cerebrospinal fluid, offers a much better prognosis than the original "open" method of operation on the plexus.

A new ventriculoscope is here described especially designed to allow exploratory and operative procedures to be carried out in the ventricles without removal of cerebrospinal fluid.

A case of nonobstructive hydrocephalus successfully operated upon with this instrument is here reported

Birth Trauma. William E. Studdiford, M.D

The anatomic relations in the head in the newborn infant and the forces which come into play during labor and their after-effects are described. Emphasis is placed on the injuries which occur in the spine and the abdominal viscera especially the liver and adrenal gland

It is pointed out that the greatest means of lessening the fetal and neonatal death rate in this group of cases lie along the lines of prevention.

The Acquisition of Language. Samuel T. Orton, M.D

Report of Four Cases of Hirschsprung's Disease in Which the Presacral Nerve Was Resected. E. J. Donovan, M.D

Four cases of Hirschsprung's disease are reported in which resection of the presacral and inferior mesenteric nerves gave very satisfactory results. All the patients had spontaneous bowel movements before leaving the hospital and have had most satisfactory results from one to three years after operation.

Erythroblastic Anemia. Adolph G. DeSanctis, M.D

Two cases of erythroblastic anemia occurring in young children of Greek and Italian families with the clinical findings and the course of the patients are described

An Unusual Case of Glomerular Nephritis With Uremia. Roger H. Dennett, M.D

To be published in a later issue of the JOURNAL OF PEDIATRICS.

The Treatment of Bronchiectasis in Children. John V. Bohrer, M.D

All palliative treatments must be definitely limited in the length of time they are used in the group of patients in whom the disease is amenable to curative treatment.

Thoracoplasty and phrenicectomy are limited in their usefulness.

Bronchoscope drainage is classified as only a palliative form of treatment.

Lobectomy is at present the only curative treatment. It still has too great a mortality but with modern technique and teamwork this will be reduced.

The Treatment of Scurvy With Ascorbic Acid. Elvira Goettsch, M.D

Three patients with infantile scurvy admitted to Babies Hospital were treated with ascorbic acid long enough for comparison with controls receiving equivalent amounts of orange juice. Serial roentgenograms were taken in an attempt to study healing of the subperiosteal lesions.

Clinical improvement was satisfactory in all the patients treated with ascorbic acid and was as effective as treatment with orange juice. Apparently pain was not relieved immediately by intravenous injection but this was difficult to evaluate in apprehensive infants. Calcification of subperiosteal hemorrhages, as judged

by roentgenographic examination, appeared at an earlier date in those patients receiving ascorbic acid. Ascorbic acid may be given intravenously to infants without untoward effect in doses as high as 400 mg.

Urology in Pediatrics Joseph F. McCarthy, M.D.

Vaccination in Anterior Poliomyelitis John A. Kolmer, M.D., Philadelphia, Pa.

Congenital Air Cyst of the Lung Harry S. Altman, M.D.

The following symptoms should lead one to suspect congenital cystic disease of the lung: unexplained attacks of dyspnea and cyanosis with signs of pulmonary emphysema, especially when the past history discloses recurrent periods of labored breathing and when there is no evidence of any pulmonary infection or trauma. X-ray pictures generally show a lowering of the diaphragm on the affected side, a displacement of the mediastinum toward the opposite side, and the encapsulated air cavities.

Ophthalmoscopic Appearance of the Nerve Head in the Newborn. Samuel Karelitz, M.D.

Chronic Pulmonary Infiltration, Probably Lipoid Cell Pneumonia. B. S. Denzer, M.D.

The history and clinical findings are described. It is pointed out that the diagnosis is difficult. The relationship of lipoid pneumonia to nutritional disturbances is discussed.

Localized Tuberculous Meningitis J. Brem, M.D.

A thirteen-month-old white female patient was admitted with a mass in the occipital region. Mucopurulent material which showed small collections of acid-fast bacilli was obtained. Inoculation into a guinea pig proved to be tubercle bacilli. Inoculation of spinal fluid also produced tuberculosis in a guinea pig. Tuberculin reactions in the patient were negative.

Refractory Rickets D. V. McCune, M.D.

It is a well-known fact that the same quantity of vitamin D does not serve to protect all infants equally well against rickets. In some cases it is necessary to employ more than the ordinarily recommended doses of cod liver oil in order to insure proper growth of bone. In these individuals rickets is said to be refractory to the conventional modes of prevention and treatment.

In considering the etiology of rickets in this instance, hereditary factors were excluded. The diet was adequate in the ordinary sense of the word. The renal function was normal. Biologic studies showed that the child was able to absorb vitamin D from the alimentary tract in a normal manner. Chemical measurements of the metabolic balance of calcium, phosphorus, and magnesium served to exclude both hyperparathyroidism and also acidosis of degree sufficient to produce severe rickets.

A satisfactory explanation for the phenomenon could not be offered. Similar cases have been reported by Park, Blackfan, Freudenberg, and others. The case was placed in the category of refractory rickets. This designation is descriptive rather than explanatory. In the patient reported, healing was promoted by mas-

five doses of viosterol. This fact suggested that the physiologic constitution of some individuals is such that although they ingest and absorb ordinary amounts of vitamin D, they still suffer from a relative deficiency of the vitamin

Cretinism. Edward S. Bimer M.D

The child was a typical cretin who had gone untreated until the age of eleven years. She was the size of an infant of about two years and of a mental age of about four months. The prognosis for any considerable improvement at this late stage is poor

Persistent Auricular Fibrillation. Lucy P. Sutton, M.D

The patient was under observation from May, 1930 when he was five years old, up to the present time, when he is nine years and nine months old. The auricular fibrillation has persisted for three years and three months. There were no rheumatic manifestations.

Healing of Lung Abscesses. Edith M. Lincoln, M.D. and Antoinette Raiz, M.D

Hereditary Hemophilia Treated With Theelin. Marshall C. Pease, M.D

October 20 at the New York Hospital

Immune Reactions Induced in Infants by the Intestinal Absorption of Antigenic Protein. Oscar M. Schloss, M.D

Studies on the Immune Response to Beta Hemolytic Streptococcus Infections. Vernon Lippard, M.D., and P. A. Johnson, M.D

The Role of the Mantoux Test in the Diagnosis of Tuberculosis in Children. Hugh Chaplin, M.D

The first part of the paper consists of a detailed description of a very carefully planned nursing and health service for a district of New York City having a population of 60,000. Included in the routine procedure is the Mantoux testing of each child at two years of age and yearly from then on as long as the test remains negative. In all positive cases roentgenograms of the chest are made and the child receives the examination and recommendations of an expert in childhood tuberculosis. The known contacts of children with x-ray indication of tuberculosis are carefully investigated for any evidence of tuberculous infection.

Of those receiving one Mantoux test 68 per cent were positive. Among 40 of the children negative the first year who received a second yearly test four were positive, i.e., had been infected during the previous year.

Twenty seven per cent of the children who were Mantoux positive at the initial test showed x-ray evidence of tuberculosis, while only 10 per cent of those Mantoux positive at the second yearly testing.

Three public health procedures are generally used for the diagnosis of tuberculosis in childhood: mass making of chest x-ray pictures of school children; following up known contacts of active cases followed in tuberculosis clinics; and routine Mantoux testing of all children beginning at an early age. The last two are the most useful. If they could be combined within one efficient public health organization much would be accomplished toward the eventual elimination of tuberculosis in childhood.

Cases of Leukemia With Onset Simulating Rheumatic Fever Carl H. Smith, M.D

A Case of Rheumatic Fever Treated by Induced Fever Katharine Dodge, M.D

Roentgenologic Evidence of Cardiac Abnormality May G. Wilson, M.D

Lipoid Pneumonia. Charles Hendee Smith, M.D

Experiences With Culture Grown Smallpox Vaccine T. Campbell Goodwin, M.D

Suppurative Pericarditis With Bilateral Empyema, Miner C. Hill, M.D

Observations on the Utilization of Parenteral Fat. Harry Gordon, M.D

Empyema With Gelatinous Exudate DeWitt Hendee Smith, M.D

A case of fibrinous empyema following serum treated lobar pneumonia due to pneumococcus Type I is presented

That the exudate was at first fibrinous with later liquefaction was substantiated by early failure to obtain pus on thoracentesis by aspiration of a plug of fibrin, by two injected air bubbles observed by roentgenograms suggesting that the bubbles were imbedded in a semisolid medium. At operation a central core of undissolved fibrin was found.

The injection of air in this case gave data of primary importance in understanding the pathology.

Chronic Ulcerative Colitis With Peritonitis Following Perforation. William C. Anderson, M.D

Tissue Response of White and Colored Children to Induced Tuberculosis Milton L. Levine, M.D, and W. H. Park, M.D

An Epidemic of Pneumococcus (Type I) Infection. Parker Dooley, M.D

Torsion of the Omentum. John W. Buckley, M.D

At operation, the right half of the omentum was found to be the site of a torsion about an inch below its attachment to the hepatic flexure and the transverse colon. The symptoms were a sudden onset of colicky abdominal pain in the right lower quadrant which became progressively more severe. Vomiting occurred

REPORT OF PEDIATRIC DEPARTMENTS IN GENERAL HOSPITALS

(Conclusion)

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES, AMERICAN ACADEMY OF PEDIATRICS

PREVIOUS reports have reviewed pertinent information concerning pediatric care among hospitals in each of the regions of the Academy of Pediatrics which have twenty four or more beds and bassinets exclusively for infants and children.

We here attempt to make a comparative and composite report formulated from the data given in the earlier reports.

TABLE I
NUMBER OF HOSPITALS

Region I	135
Region II	21
Region III	65
Region IV	14
Total	235

According to the 1934 report of the American Medical Association, there are in this country 6437 hospitals. Among this number probably about 4000 can be strictly designated as general hospitals, and about 58 per cent of all general hospitals have pediatric services of sufficient size to be eligible for consideration in our report. According to the report of the Committee on Medical Care for Children of the White House Conference more than half of the general hospitals have capacities of less than fifty beds, and 75 per cent of them have less than one hundred beds. These figures may help explain the reason why only 58 per cent of the general hospitals have twenty four or more beds and bassinets for children.

When we examine the data for the separate regions in Table I we find that Region I has more than twice as many qualified services as the next highest region which is Region III, six times as many as Region II, and almost ten times as many as Region IV. Population figures explain these differences only partially. When we consider census reports for the four regions we find that they are, according to last census, 1930, as given in Table II.

TABLE II

REGION I	REGION II	REGION III	REGION IV
12 eastern states 36,765,866	14 southern states 33,499,838	13 midwest and western states 30,527,891	10 for western states 10,860,431

Population is apportioned over vastly greater areas in Regions II, III and IV and of course there are relatively fewer cities in these areas than in Region I. Thus, if all other factors are the same, the size of the hospitals would be expected in general to be smaller in the latter three regions. Small communities usually do not have large hospitals and children's services of twenty four or more beds usually

are found only among the larger hospitals. Other factors of importance are the relative wealth of the respective regions and the greater number of medical centers such as medical schools and clinics, to be found in Regions I and III. Region IV, for instance, includes a large part of this country but possesses a population of less than one third that of either of the other three regions. In eight states of Region IV there are no hospitals having pediatric services of the size considered here, and of the total of fourteen with services found in that region twelve are in California.

TABLE III

BEDS		BASSINETS	
Region I	6835	Region I	5749
Region II	1162	Region II	601
Region III	2707	Region III	1697
Region IV	878	Region IV	505
<i>Total</i>	11,582	<i>Total</i>	8552

The White House Conference report lists about 39,837 beds for children among 4,021 general hospitals. Hospitals reported here then have about 29 per cent of this total number.

TABLE IV
TOTAL ADMISSIONS (1933)

CHILDREN		NEWBORN	
Region I	116,723	Region I	99,805
Region II	26,675	Region II	14,512
Region III	45,252	Region III	34,745
Region IV	10,425	Region IV	9,355
<i>Total</i>	189,075	<i>Total</i>	158,417

An interesting point concerning these figures is that total newborn admissions almost equal total children's admissions among these hospitals.

This fact makes the newborn departments of relatively great importance.

TABLE V
ATTENDING STAFF (PEDIATRISTS)

Region I	540	100 per cent of the hospitals have a special pediatric attending staff
Region II	85	
Region III	295	
Region IV	96	
<i>Total</i>	1016	

About one fourth of the total number of physicians especially interested in pediatrics in this country are members of the attending staffs of these hospitals.

TABLE VI
NEWBORN SERVICE UNDER SUPERVISION OF PEDIATRIC DEPARTMENT

Region I	67	50%
Region II	14	66%
Region III	31	47%
Region IV	8	57%
<i>Total</i>	120	51%

Among 1403 general hospitals replying to a questionnaire sent out by the White House Conference Committee only 56 per cent had a special attending staff for the pediatric department.

Among 809 replies to the White House Conference questionnaire 14.8 per cent reported pediatricists in charge of newborn services.

TABLE VII

HOSPITALS HAVING RESIDENTS WHOSE TIME IS EMPLOYED PART OR EXCLUSIVELY OF THE PEDIATRIC SERVICE

Region I	33
Region II	10
Region III	15
Region IV	10
<i>Total</i>	<i>68</i>

Eighty-five residents are employed among the sixty-eight hospitals, and of these fifty-six or 65 per cent, are employed exclusively in the pediatric department.

TABLE VIII

HOSPITALS HAVING INTERNS WHOSE TIME IS EXCLUSIVELY EMPLOYED IN THE PEDIATRIC DEPARTMENT

Region I	30	23%
Region II	4	10%
Region III	6	9%
Region IV	3	21%
<i>Total</i>	<i>43</i>	<i>18%</i>

TABLE IX

HOSPITALS IN WHICH THE HEAD NURSE IN CHARGE OF THE PEDIATRIC DEPARTMENT HAS HAD SPECIAL PEDIATRIC TRAINING

Region I	121	90%
Region II	15	71%
Region III	62	95%
Region IV	12	80%
<i>Total</i>	<i>210</i>	<i>89%</i>

TABLE X

HEAD NURSES WITH SPECIAL PEDIATRIC TRAINING LIMITED TO LESS THAN 6 MONTHS

Region I	8	No reply	13
Region II	4		5
Region III	9		12
Region IV	2		4
<i>Total</i>	<i>43 (20%)</i>		<i>36 (100%)</i>

Twenty per cent of the head nurses in charge of the pediatric departments have had less than six months of special pediatric training. The proportion may be still larger, as 17 per cent of the hospitals failed to answer this question.

TABLE XI

HOSPITALS HAVING SOCIAL SERVICE DEPARTMENTS AVAILABLE
TO THE PEDIATRIC DEPARTMENT

Region I	56	41%
Region II	7	33%
Region III	20	30%
Region IV	5	36%
<i>Total</i>	88	

Thirty seven per cent of all hospitals have social service departments available for use by the pediatric departments

Among a total of 4,268 hospitals replying to the White House Conference questionnaire, only 9.84 per cent reported that they had a social service department

TABLE XII

HOSPITALS HAVING A SPECIAL DIET KITCHEN

	FOR INFANTS		FOR CHILDREN	
Region I	125	92%	65	48%
Region II	14	69%	11	52%
Region III	50	77%	29	44%
Region IV	10	71%	6	43%
<i>Total</i>	199		111	

Eighty four per cent of all hospitals have special diet kitchens for infants, and 47 per cent have them for children

TABLE XIII

HOSPITALS SUPPLYING SCHOOLING AND RECREATION FOR CONVALESCENTS

	SCHOOLING		RECREATION	
Region I	46	34%	93	68%
Region II	4	19%	5	24%
Region III	20	30%	30	46%
Region IV	5	35%	6	43%
<i>Total</i>	75		134	

Thirty one per cent of all hospitals provide schooling, and 57 per cent provide recreation for convalescents

Seventy seven per cent of all hospitals have a children's dispensary

TABLE XIV

HOSPITALS HAVING A SPECIAL DISPENSARY FOR CHILDREN

Region I	113	83%
Region II	19	90%
Region III	40	61%
Region IV	11	80%
<i>Total</i>	183	

TABLE XV

HOSPITALS IN WHICH THE SAME STAFF SERVES IN BOTH HOSPITAL AND DISPENSARY

Region I	104	79%
Region II	14	69%
Region III	37	55%
Region IV	10	71%
Total	165	

In 70 per cent of all hospitals the same staff serves both hospitals and dispensary

TABLE XVI

HOSPITALS IN WHICH RESIDENTS AND INTERNS HAVE DUTIES IN THE PEDIATRIC DISPENSARY

	RESIDENTS		INTERNS	
Region I	24	73%	85	82%
Region II	8	60%	13	11%
Region III	13	87%	31	4%
Region IV	7	70%	9	6%
Total	50		138	

Among sixty-eight hospitals employing pediatric residents, 73 per cent afford the resident dispensary duties, and 53 per cent of the internes in all of the hospitals have duties in the pediatric dispensary

TABLE XVII

PERCENTAGE OF CHILDREN'S DEATHS AND NECROPSIES

	DEATHS	NECROPSIES
Region I	4.3 %	39.0%
Region II	6.1 %	21.7%
Region III	4.3 %	43.7%
Region IV	7.07%*	27.0%
General average for children's deaths		34%
General average for children's necropsies		32.4%

One state gave no reply

TABLE XVIII

PERCENTAGE OF NEWBORN DEATHS AND NECROPSIES

	DEATHS	NECROPSIES
Region I	2.9%	39.5%
Region II	5.1%	20.3%
Region III	4.1%	37.7%
Region IV	3.6%	46.0%
General average for newborn deaths		39%
General average for newborn necropsies		33.3%

One state gave no reply

COMMENTS AND CONCLUSIONS

Regions I, II, and III have about the same population yet there is a marked difference in the number of qualified pediatric services in the respective regions. Apparent reasons for this difference have been given. The same explanation may be

given for Region IV, plus the fact that the total population of that area is less than one third that of each of the first three regions

The 1934 report of the American Medical Association lists a total of 1,027,046 beds and 52,464 bassinets among 6,437 hospitals in this country. The hospitals considered in this report reserve about 1 per cent of that total number of beds for children but more than 15 per cent of that number of bassinets. As has been previously stated, questionnaires returned from 4,021 general hospitals revealed that there were available only about 39,837 beds for children, some of these not necessarily restricted to use by children. Hospitals considered in our reports have about 29 per cent of this total number.

Among a part of 1,403 general hospitals replying to the White House Conference questionnaire, there was an average of about eight beds per hospital for babies and about twelve beds for children from two to four years old. The average number of beds for children among hospitals considered in our report is forty nine, bassinets, 36. These figures indicate rather clearly that most of these 235 hospitals are fairly large general hospitals. Their total number of children's admissions for 1933 is better than 33 per cent of the total number of children's admissions to the 1,403 general hospitals of the 1929 White House Conference report.

Figures on newborn infants for the year 1933 also indicate that in general the obstetric departments of these general hospitals are large. The relative importance of the newborn departments becomes more apparent when we find newborn admissions almost equaling the children's admissions. In view of the fact that newborn departments in these hospitals are comparatively large, care and supervision in them should be as efficient as possible. Probably the most effective care of the newborn is secured when that department is under the supervision of the pediatric department. However, only 51 per cent of the hospitals have pediatric supervision of the newborn department. The highest percentage of such care occurs in Region II, the lowest, in Region III. When one compares this figure of 51 per cent to the 14.8 per cent for pediatric department supervision reported among 806 hospitals in the White House Conference report, the former figure is favorable. However, 100 per cent of the hospitals considered in this report have a special pediatric attending staff. When one examines the newborn death rate percentages for each region and particularly for individual hospitals, it becomes apparent that many departments cannot be very proud of their newborn mortality records. Pediatric supervision of newborn departments has provided favorable results in practically all instances in which it has been adopted. There are none of these hospitals which lack a pediatric staff. There must be, at most, few in which that staff could not or should not supervise the newborn department.

Data concerning pediatric internes and residents need little additional discussion except to say that about 25 per cent of the hospitals have pediatric services of sufficient size to warrant a pediatric resident and that about 65 per cent of these residents are employed full time on that service.

Head nurses in charge of a specific department, if they are to be particularly efficient in their work, should have special training in that specialty. Eleven per cent of the hospitals report that their head pediatric nurses have not had special pediatric training. Twenty per cent of those who had special training have had less than six months of it, 17 per cent did not reply, and probably a large percentage of this number should be added to the 20 per cent. The committee feels that head nurses in charge of pediatric departments should have at least six months of special pediatric training and preferably one year in that specialty.

Too few hospitals have social service departments for, or available to, the pediatric department. Certainly children's services of the size considered here must meet a

considerable number of problems in which the cooperation of a social service department would be helpful and at times almost indispensable. This is again a serious weakness among these hospitals.

We were pleasantly surprised to observe the number of hospitals which have a special diet kitchen for children, but we feel that all of them should have special diet kitchens or milk laboratories for infants. Sixteen per cent of the hospitals do not have them.

Schooling for convalescents is provided in fewer than one-third of the hospitals (31 per cent) and in as few as 19 per cent in Region II. Many of these hospitals probably have comparatively few children of school age confined for long periods of convalescence. Schooling may not be of particular importance in these instances although it should be provided in every hospital in which there are a number of convalescents.

Recreation for convalescents should also be available in each hospital. Fifty seven per cent of the hospitals report that they provide for it.

A large proportion (77 per cent) of the hospitals report that they have special pediatric out patient dispensaries, and among about 70 per cent of these the dispensary and hospital have interlocking staffs. A majority of these dispensaries are open three days each week, and those of the larger hospitals are open daily. Average dispensary attendance appears to be about twenty to thirty patients. If we allow an average of twenty five patients per dispensary with the dispensary open only three days weekly, it would mean that there are about 1 000 000 visits yearly. However many of these children's dispensaries are open daily, which would mean that as near as we can estimate there are probably at least between one and one and one-half million visits yearly to the pediatric out patient departments of 295 general hospitals. One and one-half millions more or less of dispensary visits each year would suggest that the pediatric out patient departments of general hospitals can and probably do, play an important rôle in child health problems throughout the country.

Seventy three per cent of pediatric residents and 53 per cent of the pediatric internes have duties in the dispensary. Unquestionably such duties enhance the value of a residency or internship and it is advisable that dispensary experience in pediatrics be made available to all residents and internes who desire such pediatric experience.

Death rates may be misleading if they are used as a gauge of hospital efficiency although newborn death rates we believe are an important index of the efficiency of respective obstetric and pediatric departments and particularly the efficiency of their cooperation. Region I can boast of the lowest figure in this respect.

Necropsy figures are particularly apt to reflect the spirit of serious research and scientific, efficient medical care associated with an institution. The average newborn and children's necropsy incidence for the four regions is 33 per cent, about 8 per cent higher than that reported among 1 002 hospitals replying in 1929 to the White House Conference questionnaire, but this is only about half of the percentage achieved by children's hospitals in this country. Region II makes a rather poor showing in this respect. This figure combined with their high children's and newborn death rate figures suggests that pediatricists and obstetricians in that area have a worth while problem to solve.

It is to be hoped that newborn and children's death rates may be lowered and necropsy percentages bettered in all regions.

Academy News

The American Academy of Pediatrics will hold its fifth annual meeting at the Waldorf Astoria Hotel in New York City on June 7 and 8, 1935. There will be four panel discussions on the following subjects: "Chronic Pyuria and Its Surgical Indications," under the direction of Dr. Hugh Cabot, "Prevention of Colds in Children," under the direction of Dr. L. W. Dean, "The Pituitary Gland," under the direction of Dr. R. G. Hoskins, and "Vitamin D," under the direction of Dr. E. V. McCollum. There will also be a number of round table discussions and a general meeting. It is expected that there will be a large attendance at this meeting. It will precede the meeting of the American Medical Association in Atlantic City, June 10 to 14.

News and Notes

On March 6, under the direction of Dr. Morgan Smith, of Little Rock, with the blessing of Dr. E. C. Mitchell, of Memphis, Tenn., the Arkansas State Pediatric Association was launched.

Dr. Adolph G. DeSanctis has been appointed Director of the Department of Pediatrics of the New York Post Graduate Medical School and Hospital, Columbia University.

Dr. H. E. Coe has been chosen Chief of Staff and Dr. J. I. Durand, Chief of the Pediatric Department of the Children's Orthopedic Hospital in Seattle.

At the meeting of the American Pediatric Society in Cleveland on May 2, 3, and 4, Dr. Fritz B. Talbot, Boston, was elected president, Dr. Franklin P. Gengenbach, Denver, vice president, Dr. Hugh McCulloch, St. Louis, secretary and treasurer, and Dr. Heyworth N. Sanford, Chicago, recorder editor for the ensuing year.

Professor A. J. Carlson of Chicago was a guest of the Society at the meeting.

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